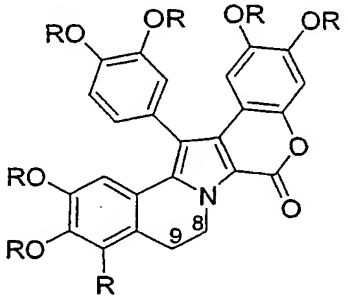
ANTITUMORAL ANALOGS OF LAMELLARINS

FIELD OF THE INVENTION

The present invention relates to antitumoral compounds, and in particular to new antitumoral analogs of lamellarins, pharmaceutical compositions containing them and their use in the treatment of cancer.

BACKGROUND OF THE INVENTION

The lamellarins are polyaromatics alkaloids originally isolated from marine sources and comprising a fused polyaromatic framework. The family of lamellarins are constituted by two basic structures:



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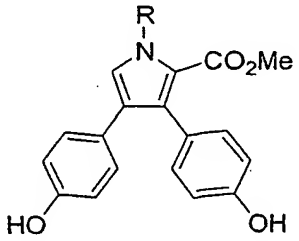

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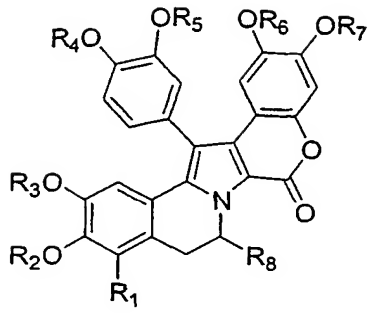
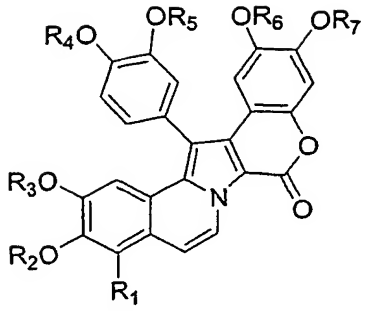
Both structures have a pyrrolic ring substituted with aryl units. The hexacyclic structure 1 is a 14-phenyl-6*H*- [1]benzopiran[4',3',4,5] pyrrolo[2,1-*a*]isoquinolin-6-one. Depending of the substituents and the presence of a double bond between C8-C9 the members of this family are designed with different letters.



	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
A	OCH_3	CH_3	CH_3	H	CH_3	CH_3	H	OH
C	OCH_3	CH_3	CH_3	H	CH_3	CH_3	H	H
E	OH	CH_3	CH_3	CH_3	H	CH_3	H	H
F	OH	CH_3	CH_3	CH_3	CH_3	CH_3	H	H
G	H	H	CH_3	CH_3	H	H	CH_3	H
I	OCH_3	CH_3	CH_3	CH_3	CH_3	CH_3	H	H
J	H	H	CH_3	CH_3	CH_3	CH_3	H	H
K	OH	CH_3	CH_3	H	CH_3	CH_3	H	H
L	H	H	CH_3	CH_3	H	CH_3	H	H
S	H	H	CH_3	H	H	H	H	H
T	OCH_3	CH_3	CH_3	CH_3	H	CH_3	H	H
U	H	CH_3	CH_3	CH_3	H	CH_3	H	H
V	OCH_3	CH_3	CH_3	CH_3	H	CH_3	H	OH
Y	H	CH_3	H	CH_3	H	CH_3	SO_3Na	H
Z	H	H	CH_3	H	H	H	CH_3	H
β	H	H	H	CH_3	H	H	H	H



	R_1	R_2	R_3	R_4	R_5	R_6	R_7
B	OCH_3	CH_3	CH_3	H	CH_3	CH_3	H
D	H	H	CH_3	H	CH_3	CH_3	H
H	H	H	H	H	H	H	H
M	OH	CH_3	CH_3	H	CH_3	CH_3	H
N	H	H	CH_3	CH_3	H	CH_3	H
W	OCH_3	CH_3	CH_3	CH_3	H	CH_3	H
X	OH	CH_3	CH_3	CH_3	H	CH_3	H
α	H	CH_3	CH_3	CH_3	H	CH_3	SO_3Na

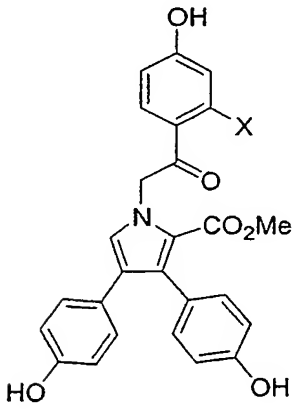
R. J. Anderson et al, *J. Am. Chem. Soc.* **1985**, *107*, 5492, describes the isolation and characterization of four polyaromatic metabolites, the lamellarins A-D, obtained from a marine prosobranch mollusc *Lamellaria sp.* The structure of lamellarin A was determined by an X-Ray crystallographic study and the structures of lamellarins B-D were assigned by interpretation of spectral data.

N. Lindquist et al, *J. Org. Chem.* **1988**, *53*, 4570, describes the isolation and characterization of four new lamellarins: E-H from the marine ascidian *Didemnum chartaceum* obtained from the Indian Ocean. The structure of lamellarin E was determined by an X-Ray crystallographic study.

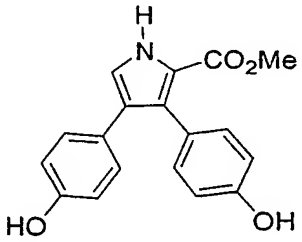
A. R. Carroll et al, *Aust. J. Chem.* **1993**, *46*, 489, isolated six new lamellarins: I, J, K, L, M and the triacetate of the lamellarin N, and four

known of this type: A, B, C, and the triacetate of lamellarin D, isolated from a marine ascidian *Didemnum sp.*

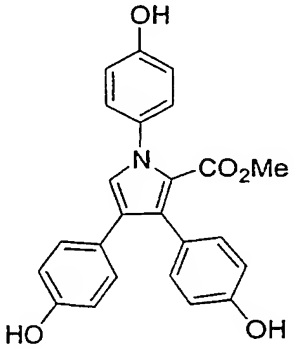
S. Urban et al, *Aust. J. Chem.* **1994**, *47*, 1919 and *Aust. J. Chem.* **1995**, *48*, 1491, described the isolation and characterization of four new lamellarins, O, P, Q, R, with the substructure type 2 from the marine sponge *Dendrilla cactos*. Later S. Urban et al, *Aust. J. Chem.* **1996**, *49*, 711, described the structure of lamellarin S from the ascidian *Didemnum sp.*



O (X= H)
P (X= OH)



Q



R

M. V. R. Reddy et al, *Tetrahedron* **1997**, *53*, 3457, isolated five new lamellarins: T, U, V, W, and X, and the first example of sulfated lamellarin, Y, isolated from the marine ascidian *Didemnum sp* obtained from the Arabian sea.

R. A. Davis et al, *J. Nat. Prod.* **1999**, *62*, 419, described one new lamellarin, Z, and various examples of sulphated lamellarins isolated from the marine ascidian *Didemnum chartaceum.*

M. V. R. Reddy et al, *J. Med. Chem.* **1999**, *42*, 1901, isolated a new lamellarin, α, isolated from the marine ascidian *Didemnum sp.*

Finally, J. Ham et al, *Bull. Korean Chem. Soc.* **2002**, *23*, 163, described the isolation and characterization of the lamellarin β obtained from a marine ascidian *Didemnum sp.*

Lamellarins C and D have been shown to cause inhibition of cell division in a fertilised sea urchin assay, whereas lamellarins I, K , and L all exhibit comparable cytoxicity against P388 and A549 cell lines in culture. Recently, lamellarin N has been shown to exhibit activity in lung cancer cell lines by acting as a Type IV microtubule poison.

Furthermore, J. L. Fernández-Puentes et al, PCT Int. Appl WO 97/01336, describe that these compounds have also cytotoxic activity on multidrug resistant cells as well as efficacy as non-toxic modulators of the multidrug resistant phenotype and, therefore, afford an attractive potential source of chemotherapeutic agents.

The limited availability of natural material has resulted in the search for alternative synthetic methods being sought for the natural compounds and related analogs. M. G. Banwell et al, Int. Patent Appl. WO 98/50365 and Int. Patent Appl. WO 99/67250 described the synthesis of lamellarin K via 1,3-dipolar cycloaddition between an alkyne and an N-ylide of isoquinolin.

Lamellarin G trimethyl ether was also synthetised by S. Ruchirawat et al, *Tetrahedron Lett.* **2001**, *42*, 1250. The synthesis involved the formation of the core pyrrolo[2,1-*a*]isoquinoline, followed by the formation of the lactone ring.

Lamellarins I and K (**1**) were obtained by L. Castedo et al, *Synlett* **2001**, *7*, 1164, by a new approach based on the 1,3-dipolar cycloaddition of a nitrone to an alkyne. The key cycloaddition yield an isoxazoline which rearranged to afford the central pyrrole ring.

F. Albericio et al, *Org. Lett* **2003**, *5*, 2959, has described a total solid-phase synthesis of Lamellarins U and L.

Ishibashi F. et al., *J.Nat.Prod.*, **2002**, 65, 500-504 describe the synthesis and structure activity relationship for some lamellarin derivatives.

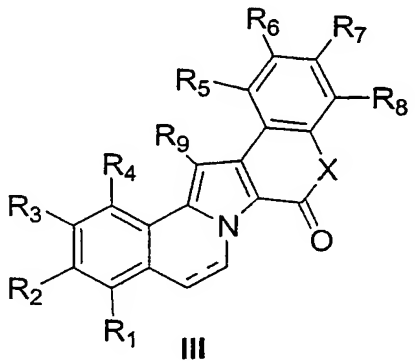
The discovery of the main target for an anticancer agent is an essential element to better understand its mechanism of action and to guide the development of clinically useful analogs. To illustrate this, one can refer to camptothecin (CPT) discovered in the early 1960s but successfully developed only a quarter of a century later when its main, and perhaps unique, molecular target was identified: topoisomerase I. The observation in 1985 that CPT stabilizes DNA-topoisomerase I complexes provided the starting point for the rational development of safe CPT analogs which culminated in the mid 1990s with the approval of topotecan and irinotecan for the treatment of ovarian and colon cancers.

The search for non-CPT topoisomerase I poisons has been very active for the past ten years but only a limited number of potent topoisomerase I poisons has been discovered.

SUMMARY OF THE INVENTION

We have found that the lamellarins represent a new and promising series of topoisomerase I inhibitors. The correlation between the capacity of the drugs to stimulate topoisomerase I-mediated DNA cleavage and their cytotoxic potential makes them useful as antitumor agents.

The present invention is directed to compounds of the general formula **III** :



III

wherein X is selected from the group consisting of N, O and S;

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are each independently selected from the group consisting of H, OH, OR´, SH, SR´, SOR´, SO_2R´, NHR´, $N(R')_2$, N=R', NHCOR´, $N(COR')_2$, $NHSO_2R$´, NO_2, $PO(R')_2$, PO_2R', C(=O)H, C(=O)R´, CO_2H, CO_2R´, $OPO(R')_2$, OPO_2R', OC(=O)H, OC(=O)R´, $N=C(R')_2$, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_1-C_{12} haloalkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl and substituted or unsubstituted heteroaromatic;

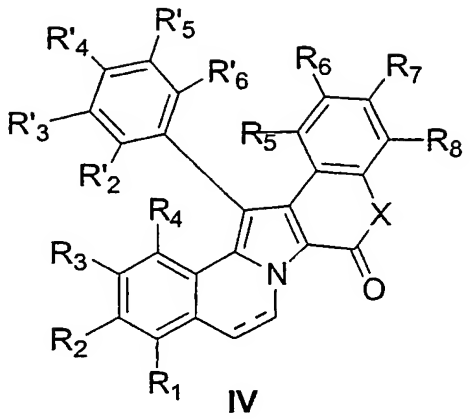
wherein each of the R' groups is independently selected from the group consisting of H, OH, NO_2, NH_2, SH, CN, halogen, =O, C(=O)H, $C(=O)CH_3$, CO_2H, C(=O)R', substituted or unsubstituted C_1-C_{18} alkyl, substituted or unsubstituted C_2-C_{18} alkenyl, substituted or unsubstituted C_2-C_{18}

alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted C_1-C_{18} alkoxyl, substituted or unsubstituted C_1-C_{18} aminoalkyl, substituted or unsubstituted C_1-C_{18} aminoacid, substituted or unsubstituted C_1-C_{18} thioalkyl, substituted or unsubstituted C_1-C_{18} alkylsulfinyl, substituted or unsubstituted C_1-C_{18} alkylsulfonyl;
wherein the pairs of groups R_1 and R_2, R_2 and R_3, R_3 and R_4, R_3 and R_9, R_4 and R_9, R_9 and R_5, R_9 and R_6, or R_6 and R_7, R_7 and R_8 may be joined into a carbocyclic or heterocyclic ring system;
and the dotted line represents an single or double bond;
or a pharmaceutically acceptable salt, derivative, prodrug or stereoisomer thereof.

We exclude compounds that are known lamellarins, especially known lamellarins described in the literature acknowledged in the present introduction, and more especially lamellarins A-N and S-Z or lamellarins α or β, as well as lamellarin D, K, L, M or N triacetate, lamellarin G trimethyl ether and compounds in WO 9850365. In this respect, we explicitly incorporate by specific reference each of the prior art documents mentioned in the present introduction, particularly for any disclsoure of a known compound which needs to be excluded from the repsent claims.

Preferred Embodiments

Preferred compounds of this invention are those of formula **IV** :



IV

wherein R_1-R_8 are as defined above and R'_2-R'_6 and the dotted line have the same definitions as for R_1-R_8 . In this respect, appropriate pairs of R'_2-R'_6 may be joined into a carbocyclic or heterocyclic ring system.

In formula **III** or **IV** X is preferably O or NH, most preferably O.

Preferred compounds are those that have a double bond between C-8 and C-9 (dotted line), they have shown higher antitumoral activity.

In a preferred aspect of the invention each of R_1-R_8 is independently selected from H, OR' , OC(=O)R'.

R_3 is preferably selected from the group consisting of H, OH, alkoxy, most preferably methoxy.

R_4, R_5, R_6 and R_8 are preferably each independently selected from the group consisting of H or alkoxy, most preferably they are H. Suitably at least 2, 3 or preferably all 4 of R_4, R_5, R_6 and R_8 are the same, and R_3 is preferably that group.

R_1, R_2 and R_7 are preferably each independently selected from the group consisting of H, OH, alkoxy, OC(=O)R', SO_2R', $PO(R')_2$, Alkyl, NO_2, NH_2.

In a most preferred embodiment R_1, R_2 and R_7 are OC(=O)R' wherein R' is a substituted or unsubstituted aminoacid or aminoacids chain, preferably with a cationic group. Suitably at least 2, or preferably all 3 of R_1, R_2, and R_7 are the same.

In formula **IV** R'_2, R'_3 and R'_6 are preferably each independently selected from the group consisting of H or alkoxy, most preferably H; and R'_5 is preferably selected from the group consisting of H or alkoxy, most preferably methoxy.

R'_4 is preferably selected from the group consisting of H, OH, alkoxy, OC(=O)R', SO_2R', $PO(R')_2$, Alkyl, NO_2, NH_2. Most preferably R'_4 is C(=O)R' wherein R' is a substituted or unsubstituted aminoacid or aminoacids chain, preferably with a cationic group.

Often R'_4, R_7 and either R_1 or R_2 is the same.

Any of the groups with a protectable hydroxy or amino subsituent may be in protected form, using available protecting groups.

Suitable protecting groups for phenols and hydroxy groups include ethers and esters, such as alkyl, alkoxyalkyl, aryloxyalkyl, alkoxyalkoxyalkyl, alkylsilylalkoxyalkyl, alkylthioalkyl, arylthioalkyl, azidoalkyl, cyanoalkyl, chloroalkyl, heterocyclic, arylacyl, haloarylacyl, cycloalkylalkyl, alkenyl, cycloalkyl, alyklarylalkyl, alkoxyarylalkyl, nitroarylalkyl, haloarylalkyl, alkylaminocarbonylarylalkyl, alkylsulfinylarylalky, alkylsilyl and other ethers, and arylacyl, aryl alkyl carbonate, aliphatic carbonate, alkylsulfinylarlyalkyl carbonate, alkyl carbonate, aryl haloalkyl carbonate, aryl alkenyl carbonate, aryl carbamate, alkyl phosphinyl, alkylphosphinothioyl, aryl phosphinothioyl, aryl alkyl sulphonate and other esters. Such groups

may optionally be substituted with the previously mentioned groups in R^1.

Suitable protecting groups for amines include carbamates, amides, and other protecting groups, such as alkyl, arylalkyl, sulpho- or halo-arylalkyl, haloalkyl, alkylsilylalkyl, arylalkyl, cycloalkylalkyl, alkylarylalkyl, heterocyclylalkyl, nitroarylalkyl, acylaminoalkyl, nitroaryldithioarylalkyl, dicycloalkylcarboxamidoalkyl, cycloalkyl, alkenyl, arylalkenyl, nitroarylalkenyl, heterocyclylalkenyl, heterocyclyl, hydroxyheterocyclyl, alkyldithio, alkoxy- or halo- or alkylsulphinyl arylalkyl, hetercyclylacyl, and other carbamates, and alkanoyl, haloalkanoyl, arylalkanoyl, alkenoyl, heterocyclylacyl, aroyl, arylaroyl, haloaroyl, nitroaroyl, and other amides, as well as alkyl, alkenyl, alkylsilylalkoxyalkyl, alkoxyalkyl, cyanoalkyl, heterocyclyl, alkoxyarylalkyl, cycloalkyl, nitroaryl, arylalkyl, alkoxy- or hydroxy-arylalkyl, and many other groups. Such groups may optionally be substituted with the previously mentioned groups in R^1.

Examples of such protecting groups are given in the following tables.

protection for -OH group

ethers	abbreviation
methyl	
methoxymethyl	MOM
benzyloxymethyl	BOM
methoxyethoxymethyl	MEM
2-(trimethylsilyl)ethoxymethyl	SEM
methylthiomethyl	MTM
phenylthiomethyl	PTM
azidomethyl	
cyanomethyl	
2,2-dichloro-1,1-difluoroethyl	
2-chloroethyl	
2-bromoethyl	
tetrahydropyranyl	THP

1-ethoxyethyl	EE
phenacyl	
4-bromophenacyl	
cyclopropylmethyl	
allyl	
propargyl	
isopropyl	
cyclohexyl	
t-butyl	
benzyl	
2,6-dimethylbenzyl	
4-methoxybenzyl	MPM or PMB
o-nitrobenzyl	
2,6-dichlorobenzyl	
3,4-dichlorobenzyl	
4-(dimethylamino)carbonylbenzyl	
4-methylsuflinylbenzyl	Msib
9-anthrylmethyl	
4-picolyl	
heptafluoro-*p*-tolyl	
tetrafluoro-4-pyridyl	
trimethylsilyl	TMS
t-butyldimethylsilyl	TBDMS
t-butyldiphenylsilyl	TBDPS
triisopropylsilyl	TIPS
esters	
aryl formate	
aryl acetate	
aryl levulinate	
aryl pivaloate	ArOPv
aryl benzoate	
aryl 9-fluorocarboxylate	
aryl methyl carbonate	
1-adamantyl carbonate	
t-butyl carbonate	BOC-OAr
4-methylsulfinylbenzyl carbonate	Msz-Oar
2,4-dimethylpent-3-yl carbonate	Doc-Oar
aryl 2,2,2-trichloroethyl carbonate	
aryl vinyl carbonate	
aryl benzyl carbonate	
aryl carbamate	
dimethylphosphinyl	Dmp-OAr

dimethylphosphinothioyl	Mpt-OAr
diphenylphosphinothioyl	Dpt-Oar
aryl methanesulfonate	
aryl toluenesulfonate	
aryl 2-formylbenzenesulfonate	

protection for the -NH_2 group

carbamates	abbreviation
methyl	
ethyl	
9-fluorenylmethyl	Fmoc
9-(2-sulfo)fluroenylmethyl	
9-(2,7-dibromo)fluorenylmethyl	
17-tetrabenzo[*a,c,g,i*]fluorenylmethyl	Tbfmoc
2-chloro-3-indenylmethyl	Climoc
benz[*f*]inden-3-ylmethyl	Bimoc
2,7-di-*t*-butyl[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl	DBD-Tmoc
2,2,2-trichloroethyl	Troc
2-trimethylsilylethyl	Teoc
2-phenylethyl	hZ
1-(1-adamantyl)-1-methylethyl	Adpoc
2-chlooethyl	
1,1-dimethyl-2-chloroethyl	
1,1-dimethyl-2-bromoethyl	
1,1-dimethyl-2,2-dibromoethyl	DB-*t*-BOC
1,1-dimethyl-2,2,2-trichloroethyl	TCBOC
1-methyl-1-(4-biphenyl)ethyl	Bpoc
1-(3,5-di-*t*-butylphenyl)-1-1-methylethyl	*t*-Burmeoc
2-(2'-and 4'-pyridyl)ethyl	Pyoc
2,2-bis(4'-nitrophenyl)ethyl	Bnpeoc
n-(2-pivaloylamino)-1,1-dimethylethyl	
2-[(2-nitrophenyl)dithio]-1-phenylethyl	NpSSPeoc
2-(*n,n*-dicyclohexylcarboxamido)ethyl	
t-butyl	BOC
1-adamantyl	1-Adoc
2-adamantyl	2-Adoc
vinyl	Voc
allyl	Aloc or Alloc
1-isopropylallyl	Ipaoc
cinnamyl	Coc
4-nitrocinnamyl	Noc
3-(3'-pyridyl)prop-2-enyl	Paloc

8-quinolyl	
n-hydroxypiperidinyl	
alkyldithio	
benzyl	Cbz or Z
p-methoxybenzyl	Moz
p-nitrobenzyl	PNZ
p-bromobenzyl	
p-chlorobenzyl	
2,4-dichlorobenzyl	
4-methylsulfinylbenzyl	Msz
9-anthrylmethyl	
diphenylmethyl	
phenothiazinyl-(10)-carbonyl	
n'-*p*-toluenesulfonylaminocarbonyl	
n'-phenylaminothiocarbonyl	
amides	
formamide	
acetamide	
chloroacetamide	
trifluoroacetamide	TFA
phenylacetamide	
3-phenylpropanamide	
pent-4-enamide	
picolinamide	
3-pyridylcarboxamide	
benzamide	
p-phenylbenzamide	
n-phthalimide	
n-tetrachlorophthalimide	TCP
4-nitro-*n*-phthalimide	
n-dithiasuccinimide	Dts
n-2,3-diphenylmaleimide	
n-2,5-dimethylpyrrole	
n-2,5-bis(triisopropylsiloxyl)pyrrole	BIPSOP
n-1,1,4,4-	STABASE
tetramethyldisiliazacyclopentante adduct	
1,1,3,3-tetramethyl-1,3-disilaisoindoline	BSB
special -NH protective groups	
n-methylamine	
n-*t*-butylamine	
n-allylamine	
n-[2-trimethylsilyl)ethoxy]methylamine	SEM
n-3-acetoxypropylamine	

n-cyanomethylamine	
n-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl)amine	
n-2,4-dimethoxybenzylamine	Dmb
2-azanorbornenes	
n-2,4-dinitrophenylamine	
n-benzylamine	Bn
n-4-methoxybenzylamine	MPM
n-2,4-dimethoxybenzylamine	DMPM
n-2-hydroxybenzylamine	Hbn
n-(diphenylmethyl)amino	DPM
n-bis(4-methoxyphenyl)methylamine	
n-5-dibenzosuberylamine	DBS
n-triphenylmethylamine	Tr
n-[(4-methoxyphenyl)diphenylmethyl]amino	MMTr
n-9-phenylflurenylamine	Pf
n-ferrocenylmethylamine	Fcm
n-2-picolylamine *n'*-oxide	
n-1,1-dimethylthiomethyleneamine	
n-benzylideneamine	
n-*p*-methoxybenzylideneamine	
n-diphenylmethyleneamine	
n-(5,5-dimethyl-3-oxo-1-cyclohexenyl)amine	
n-nitroamine	
n-nitrosoamine	
diphenylphosphinamide	Dpp
dimethylthiophosphinamide	Mpt
diphenylthiophosphinamide	Ppt
dibenzyl phosphoramidate	
2-nitrobenzenesulfenamide	Nps
n-1-(2,2,2-trifluoro-1,1-diphenyl)ethylsufenamide	TDE
3-nitro-2-pyridinesulfenamide	Npys
p-toluenesulfonamide	Ts
benzenesulfonamide	

It is preferred that at least one of R_1-R_8 and R'_2-R'_6 is not H, OH, OCH_3, SO_3Na, most preferably at least two are not H, OH, OCH_3, SO_3Na. It is also preferred that at least one of these substituents has at least 2, more preferably at 3, yet more preferably at least 4 carbon atoms. In

particular, we prefer that R'_4 and R_7, and possibly also R_1, have these minimal numbers of carbon atoms.

Antitumoral activities of these compounds include leukaemias, lung cancer, colon cancer, kidney cancer, prostate cancer, pancreatic cancer, cervix cancer, ovarian cancer, breast cancer, sarcomas and melanomas.

In another aspect the present invention is directed to pharmaceutical compositions useful as antitumor agents that contain as active ingredient a compound or compounds of the invention or a pharmaceutically acceptable salt, derivative, prodrug or stereoisomer thereof and a pharmaceutically acceptable carrier.

The present invention is also directed to the use compounds of the general formula **III** above or pharmaceutically acceptable salts, derivatives, prodrugs or stereoisomers thereof in the treatment of cancer, or in the preparation of a medicament for the treatment of cancer.

In a further aspect the present invention is also directed to the use of compounds of the general formula **III** above or pharmaceutically acceptable salts, derivatives, prodrugs or stereoisomers thereof as topoisomerase I inhibitors.

DETAILED DESCRIPTION OF THE INVENTION.

Fifteen years of efforts in targeting topoisomerase I for the discovery of anticancer agents have lead to the identification of several families of compounds capable of stabilizing DNA-topoisomerase I covalent complexes. The lead series is with no doubt the camptothecin family

with two drugs, topotecan and irinotecan, approved for cancer treatment and several second (e.g. lurtotecan, exatecan) and third (e.g. diflomotecan) generations of camptothecin analogs currently in clinical trials. However, apart from the camptothecins, only a few topoisomerase I poisons have reached phase I clinical trials. Promising results have been reported with glycosyl indolocarbazoles but so far there is still no non-CPT topoisomerase I poisons in advanced clinical trials. The need for new series of topoisomerase I poisons remains pressing.

We have now surprisingly found that the natural lamellarins and their analogs are potent Topoisomerase I inhibitors, and that they exhibit sequence specificity profiles distinct from Camptothecin which is a well know Topoisomerase I inhibitor and chemotherapeutic agent, suggesting that they recognize differently with the topoisomerase I-DNA interface.

Therefore the invention is directed at compounds of formula **III** as defined above, their use as antitumoral agents and pharmaceutical compositions containing them.

The following gives guidance for the substituents in formulae **III** and **IV**:

Preferred R' groups are present in groups of formula R', COR' or OCOR' and include alkyl or alkenyl, that may be substituted at one or more available positions by one or more suitable groups, e.g., halogen such as fluoro, chloro, bromo and iodo, especially ω-chloro or perfluoro; aminoalkyl groups such as groups having one or more N atoms and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms, and especially including substituted or unsubstituted aminoacids or aminoacid chains, notably glycine, alanine, arginine, asparagine,

asparaginic acid, cystein, glutamine, glutamic acid, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine or valine, especially protected forms of such amino acids; carbocylic aryl having 6 or more carbons, particularly phenyl; and aralkyl such as benzyl; heterocyclic groups including heteroalicyclic and heteroaromatic groups, especially with 5 to 10 ring atoms of which 1 to 4 are heteroatoms, more preferably heterocyclic groups with 5 or 6 ring atoms and 1 or 2 heteratoms or with 10 ring atoms and 1 to 3 heteroatoms, the heterocyclic groups optionally being substituted with one or more of the subsitituents permitted for R' and especially amino such as dimethylamino or with keto.

Suitable halogen substituents in the compounds of the present invention include F, Cl, Br and I.

Alkyl groups preferably have from 1 to 24 carbon atoms. One more preferred class of alkyl groups has 1 to about 12 carbon atoms, yet more preferably 1 to about 8 carbon atoms, still more preferably 1 to about 6 carbon atoms, and most preferably 1, 2, 3 or 4 carbon atoms. Another more preferred class of alkyl groups has 12 to about 24 carbon atoms, yet more preferably 12 to about 18 carbon atoms, and most preferably 13, 15 or 17 carbon atoms. Methyl, ethyl and propyl including isopropyl are particularly preferred alkyl groups in the compounds of the present invention. As used herein, the term alkyl, unless otherwise modified, refers to both cyclic and noncyclic groups, although cyclic groups will comprise at least three carbon ring members.

Preferred alkenyl and alkynyl groups in the compounds of the present invention have one or more unsaturated linkages and from 2 to about

12 carbon atoms, more preferably 2 to about 8 carbon atoms, still more preferably 2 to about 6 carbon atoms, even more preferably 2, 3 or 4 carbon atoms. The terms alkenyl and alkynyl as used herein refer to both cyclic and noncyclic groups, although straight or branched noncyclic groups are generally more preferred.

Alkylidene groups may be branched or unbranched and preferably have from 1 to 12 cabon atoms. One more preferred class of alkylidene groups has from 1 to about 8 carbon atoms, yet more preferably from 1 to about 6 carbon atoms, and most preferably 1, 2, 3 or 4 carbon atoms. Methylidene, ethylidene and propylidene including isopropylidene are particularly preferred alkylidene groups in the compounds of the present invention.

Preferred alkylsulfinyl groups in the compounds of the present invention include those groups having one or more sulfoxide (SO) groups and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms. Alkylsulfinyl groups having 1, 2, 3 or 4 carbon atoms are particularly preferred.

Preferred alkylsulfonyl groups in the compounds of the present invention include those groups having one or more sulfonyl (SO_2) groups and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms. Alkylsulfonyl groups having 1, 2, 3 or 4 carbon atoms are particularly preferred.

Preferred aminoalkyl groups include those groups having one or more primary, secondary and/or tertiary amine groups, and from 1 to about 12 carbon atoms, more preferably 1 to about 8 carbon atoms, still more

preferably 1 to about 6 carbon atoms, even more preferably 1, 2, 3 or 4 carbon atoms. Secondary and tertiary amine groups are generally more preferred than primary amine moieties.

Suitable heterocyclic groups include heteroaromatic and heteroalicyclic groups. Suitable heteroaromatic groups in the compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms and include, e.g., coumarinyl including 8-coumarinyl, quinolinyl including 8-quinolinyl, pyridyl, pyrazinyl, pyrimidyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, indolyl, benzofuranyl and benzothiazol. Suitable heteroalicyclic groups in the compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms and include, e.g., tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholino and pyrrolindinyl groups.

Suitable carbocyclic aryl groups in the compounds of the present invention include single and multiple ring compounds, including multiple ring compounds that contain separate and/or fused aryl groups. Typical carbocyclic aryl groups contain 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms. Specifically preferred carbocyclic aryl groups include phenyl including substituted phenyl such as 2-substituted phenyl, 3-substituted phenyl, 2.3-substituted phenyl, 2.5-substituted phenyl, 2.3.5-substituted and 2.4.5-substituted phenyl, including where one or more of the phenyl substituents is an electron-withdrawing group such as halogen, cyano, nitro, alkanoyl, sulfinyl, sulfonyl and the like; naphthyl including 1-naphthyl and 2-naphthyl; biphenyl; phenanthryl; and anthracyl.

References herein to substituted R' groups in the compounds of the present invention refer to the specified moiety, typically alkyl or alkenyl, that may be substituted at one or more available positions by one or

more suitable groups, e.g., halogen such as fluoro, chloro, bromo and iodo; cyano; hydroxyl; nitro; azido; alkanoyl such as a C1-6 alkanoyl group such as acyl and the like; carboxamido; alkyl groups including those groups having 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms and more preferably 1-3 carbon atoms; alkenyl and alkynyl groups including groups having one or more unsaturated linkages and from 2 to about 12 carbon or from 2 to about 6 carbon atoms; alkoxy groups having those having one or more oxygen linkages and from 1 to about 12 carbon atoms or 1 to about 6 carbon atoms; aryloxy such as phenoxy; alkylthio groups including those moieties having one or more thioether linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; alkylsulfinyl groups including those moieties having one or more sulfinyl linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; alkylsulfonyl groups including those moieties having one or more sulfonyl linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; aminoalkyl groups such as groups having one or more N atoms and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; carbocylic aryl having 6 or more carbons, particularly phenyl (e.g., R being a substituted or unsubstituted biphenyl moiety); and aralkyl such as benzyl; heterocyclic groups including heteroalicyclic and heteroaromatic groups, especially with 5 to 10 ring atoms of which 1 to 4 are heteroatoms, more preferably heterocyclic groups with 5 or 6 ring atoms and 1 or 2 heteratoms or with 10 ring atoms and 1 to 3 heteroatoms.

As further guidance, we prefer as substituents for R_1-R_9 and R'_2-R'_6:

amino acids and peptides

(*L*)-Val-OH; (*L*)-N-Boc-Val-OH

(*D*)-Val-OH; (*D*)-N-Boc-Val-OH

(*L*)-Ala-OH; (*L*)-N-Boc-Ala-OH; (*L*)-N-Alloc-Ala-OH; (*L*)-N-Fmoc-Ala-OH

(*L*)-Phe-OH; (*L*)-N-Boc-Phe-OH

(*L*)-N-Boc-Lys(Cbz)-OH

(*L*)-Leu-OH; (*L*)-N-Boc-Leu-OH

(*L*)-Pro-OH; (*L*)-N-Boc-Pro-OH

(*L*)-Trp-OH; (*L*)-N-Boc-Trp-OH

(*L*)-Ile-OH; (*L*)-N-Boc-Ile-OH

(*L*)-Ser(Bn)-OH; (*L*)-N-Boc-Ser(Bn)-OH

(*L*)-Cys(Fm)-OH; (*L*)-N-Boc-Cys(Fm)-OH

(*L*)-N-Boc-β-Leu-OH

(*L*)-N-Boc-Lys(Boc)Gly-OH

(*L*)-AlaAla-OH; (*L*)-N-Boc-AlaAla-OH

Esters

Hydrocinnamoyl

Cyclohexylpropyl

Methanosulfonyl (Ms)

Trifluoromethanosulfonyl (Tf)

Octanoyl

Biotin

Acetyl

Coumarin 3-carboxyl

2[(4-fluorophenyl)thio]acetyl

4-fluorenecarboxyl

9H-fluorene-4-carboxyl

2,3,4,5-Tetrafluorobenzoyl

4-Pentynoyl

4-Methyl cinnamoyl

3,5-Dibromobenzoyl

5(2-Phenyleth-1-ynyl)nicotinyl

6-(Boc-amino)caproyl

6-Aminocaproyl
3-(Boc-amino)propyl
3-Aminopropyl

Ethers
Methyl
Isopropyl
Benzyl
4-Methoxybenzyl
Methoxymethyl
Methilenedioxy
Tert-butyldiphenylsilyl

Nitrogen compounds
Nitro
Amino
Methylamino
Dimethylamino
Benzophenone imine

Phosphates
Diethyl phosphate

Halogens
Cl, Br, I

Cyanides
CN

The term "pharmaceutically acceptable salts, derivatives, prodrugs" refers to any pharmaceutically acceptable salt, ester, solvate, hydrate or

any other compound which, upon administration to the recipient is capable of providing (directly or indirectly) a compound as described herein. However, it will be appreciated that non-pharmaceutically acceptable salts also fall within the scope of the invention since those may be useful in the preparation of pharmaceutically acceptable salts. The preparation of salts, prodrugs and derivatives can be carried out by methods known in the art.

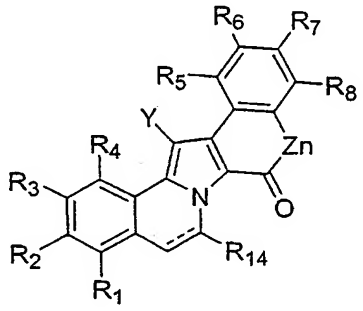
For instance, pharmaceutically acceptable salts of compounds provided herein are synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts are, for example, prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent or in a mixture of the two. Generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol or acetonitrile are preferred. Examples of the acid addition salts include mineral acid addition salts such as, for example, hydrochloride, hydrobromide, hydroiodide, sulphate, nitrate, phosphate, and organic acid addition salts such as, for example, acetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, methanesulphonate and p-toluenesulphonate. Examples of the alkali addition salts include inorganic salts such as, for example, sodium, potassium, calcium and ammonium salts, and organic alkali salts such as, for example, ethylenediamine, ethanolamine, N,N-dialkylenethanolamine, triethanolamine and basic aminoacids salts.

The compounds of the invention may be in crystalline form either as free compounds or as solvates (e.g. hydrates) and it is intended that both forms are within the scope of the present invention. Methods of solvation are generally known within the art.

Any compound that is a prodrug of a compound of formula **III** is within the scope and spirit of the invention. The term "prodrug" is used in its broadest sense and encompasses those derivatives that are converted in vivo to the compounds of the invention. Such derivatives would readily occur to those skilled in the art, and include, for example, compounds where a free hydroxy group is converted into an ester derivative.

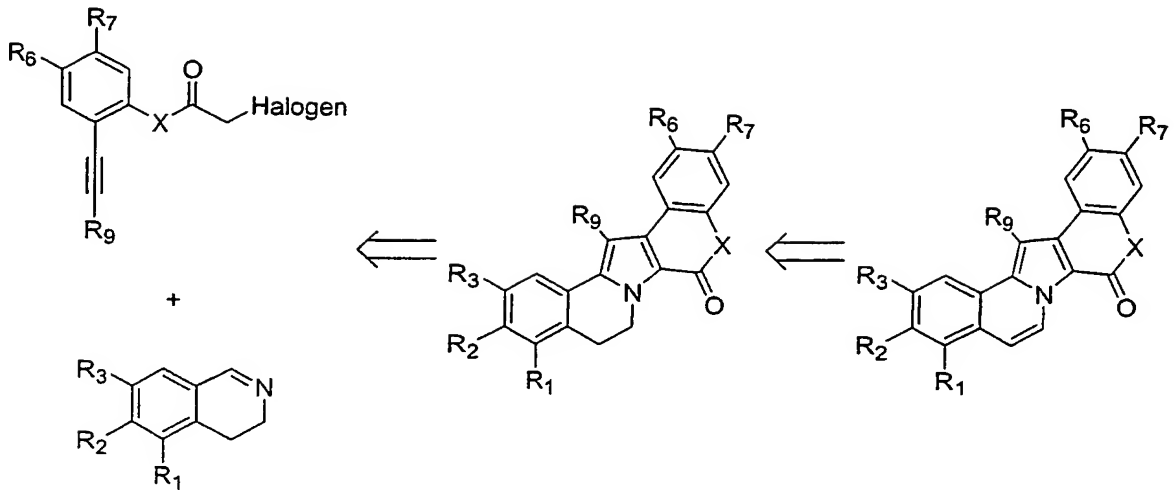
The compounds of the present invention represented by the above described formula **III** may include enantiomers depending on their asymmetry or diastereoisomers. The single isomers and mixtures of the isomers fall within the scope of the present invention.

The compound of the present invention can be prepared synthetically from the intermediate compound **Va** described in the PCT Int. Appl WO 98 50365. Numerous active antitumoral compounds have been prepared from this compound and it is believed that many more compounds can be formed in accordance with the teachings of the present disclosure.



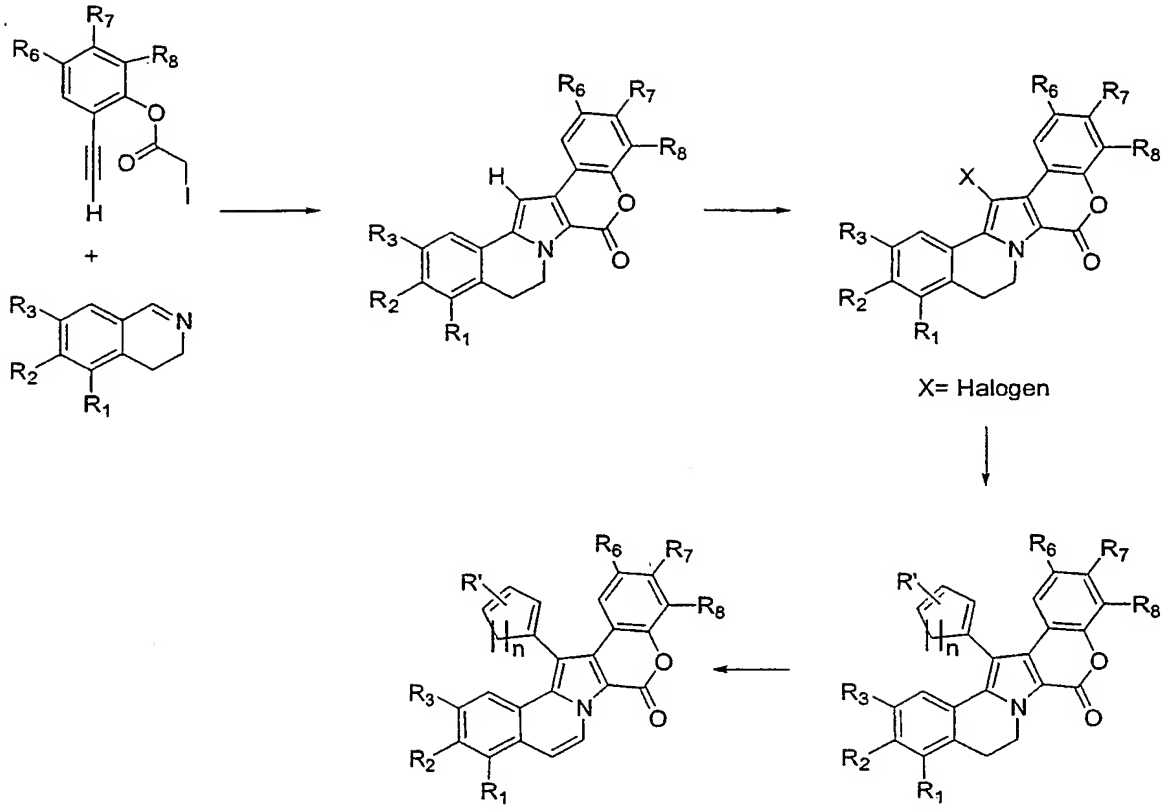
Va

The compounds of formula **III** can be prepared from simple starting materials based on the following retrosynthesis.

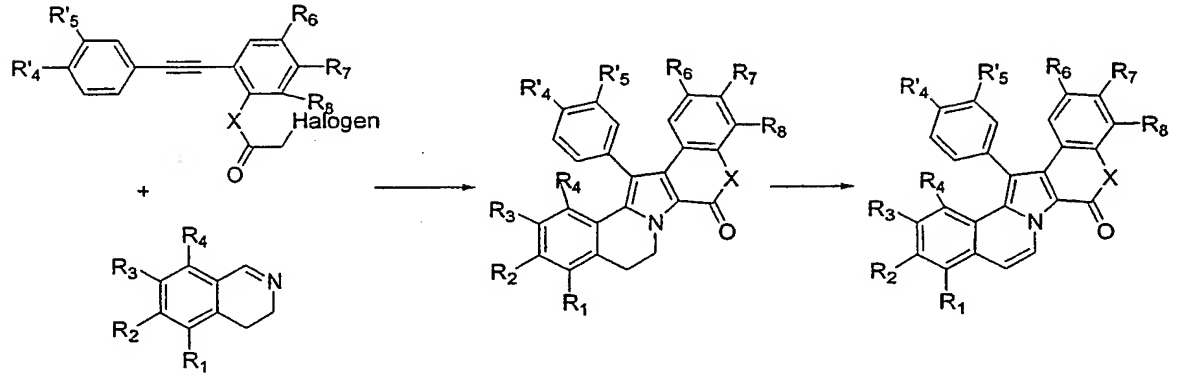


Dependent on the choice of the R substituents of the starting materials or the chemical transformations into different definitions of this R, the methodology can provide access to a wide range of Lamellarins analogs as exemplified herein.

The preparation of compounds of general formula **III** is illustrated below for R_9 as H, Halogen, substituted or unsubstituted aryl or substituted or unsubstituted heteroaromatic.



The preparation of compounds of general formula **IV** is illustrated below:



Further details are given in the the experimental procedures and the physicochemical characteristics of the compounds in the examples.

Another especially preferred embodiment of the present invention is pharmaceutical compositions useful as antitumor agents which contain as active ingredient a compound or compounds of the invention, as well as the processes for their preparation.

An important feature of the above described compounds of formula **III** is their bioactivity and in particular their cytotoxic activity. With this invention we provide novel pharmaceutical compositions of compounds of general formula **III** that possess cytotoxic activity, and their use as antitumor agents. Thus the present invention further provides pharmaceutical compositions comprising a compound of this invention, a pharmaceutically acceptable salts, derivatives, prodrugs or stereoisomers thereof with a pharmaceutically acceptable carrier.

Examples of pharmaceutical compositions include any solid (tablets, pills, capsules, granules etc.) or liquid (solutions, suspensions or emulsions) with suitable composition for oral, topical or parenteral administration.

Administration of the compounds or compositions of the present invention may be any suitable method, such as intravenous infusion, oral preparation, intraperitoneal and intravenous preparation. We prefer that infusion times of up to 24 hours are used, more preferably 2-12 hours, with 2-6 hours most preferred. Short infusion times which allow treatment to be carried out without an overnight stay in hospital are especially desirable. However, infusion may be 12 to 24 hours or even longer if required. Infusion may be carried out at suitable intervals of say 1 to 4 weeks. Pharmaceutical compositions containing compounds of the invention may be delivered by liposome or

nanosphere encapsulation, in sustained release formulations or by other standard delivery means.

The correct dosage of the compounds will vary according to the particular formulation, the mode of application, and the particular situs, host and tumour being treated. Other factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

The compounds and compositions of this invention may be used with other drugs to provide a combination therapy. The other drugs may form part of the same composition, or be provided as a separate composition for administration at the same time or a different time.

Antitumoral activities of these compounds include among others leukaemias, lung cancer, colon cancer, kidney cancer, prostate cancer, ovarian cancer, breast cancer, pancreas cancer, cervix cancer, sarcomas and melanomas.

The present invention will be further explained with the following examples. These examples are illustrative of the present invention and should not not be interpreted as limitative.

EXAMPLES

Example 1: Synthesis of compounds 1-240

General Procedure A

A 0.15M suspension of the corresponding Isopropoxylated-Lamellarin (1 eq.) and $AlCl_3$ (1.3 eq. per isopropoxy group) in anhydrous dichloromethane was stirred at room temperature until the reaction was completed (2 to 6h) under Argon atmosphere. Methanol was added, the solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel to provide the corresponding Lamellarin.

General Procedure B

A solution of anhydrous dichloromethane/TFA (3:1) was added to the corresponding Boc-aminoacid-Lamellarin (0.01M) at 0°C under Argon atmosphere. The reaction mixture was stirred at room temperature for 1h. The solvent was evaporated under reduced pressure and the mixture was treated with dichloromethane in order to remove the remaining TFA. After final evaporation to dryness, the corresponding Lamellarin was collected by triturating and filtrating in ethyl ether.

General Procedure C

A solution of the corresponding Boc-aminoacid-Lamellarin in a 3.0M solution of HCl in ethyl acetate was stirred at room temperature for 30 min. The resulting suspension was filtered and the solid was washed with ethyl acetate and hexanes to provide the corresponding Lamellarin.

General Procedure D

To a 0.01M suspension of Lamellarin (1 eq.) in anhydrous dichloromethane, the corresponding carboxylic acid (2 eq. per hydroxy group), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2

eq. per hydroxy group) and dimethyl-aminopyridine (0.2 eq. per hydroxy group) were added. The mixture was stirred under argon atmosphere at room temperature for 6h. The resulting solution was diluted with dichloromethane, washed with water and saturated sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate and the solvent removed under vacuum. The residue was purified by chromatography on silica gel to provide the corresponding Lamellarin.

General Procedure E

A 0.02M solution of the corresponding Lamellarin (1 eq.) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.3 eq.) in chloroform was heated at 65°C until the reaction was completed. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The residue was purified by chromatography on silica gel to provide the corresponding Lamellarin.

General Procedure F

To a 0.01M solution of Lamellarin (1 eq.) in dichloromethane, pyridine (1.1 eq. per hydroxy group) and the corresponding acid chloride (1.1 eq. per hydroxy group) were added under argon atmosphere and stirred at room temperature for 3h. The reaction mixture was washed with saturated solution of sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel to provide the corresponding Lamellarin.

General Procedure G

Iodo-acetic acid 5-isopropoxy-2-(4-isopropoxy-3-methoxy-phenylethynyl)-4-methoxy-phenyl ester (1 eq.) was added in one portion to a 0.1M solution of the corresponding dihydro-isoquinoline or isoquinoline (1.1 eq.) in anhydrous dimethylacetamide under argon atmosphere. . The solution was stirred at room temperature for 14 hours, then triethylamine (1.1 eq.) was added and the reaction mixture was heated at 80 °C for 19 hours. The mixture was cooled, Fremy´s Salt (1.1eq) and sodium carbonate saturated solution was added and the suspension was stirred for 1 hour. The mixture was treated with sodium bicarbonate saturated solution and extracted with dichloromethane. The organic layers were dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The resulted residue was purified by chromatography on silica gel to provide the corresponding Lamellarin.

General Procedure H

Iodo-acetic acid 5-isopropoxy-2-(4-isopropoxy-3-methoxyphenyl-ethynyl)-4-methoxy-phenyl ester (1 eq.) was added in one portion to a 0.1M solution of the corresponding dihydro-isoquinoline or isoquinoline (1.1 eq.) in dry 1,2-dichloroethane under argon atmosphere. The solution was stirred at room temperature for 14 hours, then diisopropylethylamine (1.1 eq.) was added and the reaction mixture was heated at 85 °C for 32 hours. The resulting mixture was cooled, silica gel (1 g per mmol) was added and the solvent was evaporated under reduced pressure. The resulted residue was subjected to flash chromatography on silica gel (sequential elution with 5:5:1 to 5:5:2 hexane-dichloromethane-ether) to provide the corresponding Lamellarin.

General Procedure I

To a 0.015M suspension of the corresponding Lamellarin (1 eq.) in anhydrous dichloromethane at 0°C, N-phenyltrifluoro-methanesulfonimide (4 eq.), triethylamine (7 eq.) and dimethyl amino-pyridine (0.2 eq.) were added and the mixture was stirred to room temperature for 3h. The mixture was diluted with dichloromethane, washed with sodium bicarbonate saturated solution, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by chromatography on silica gel to provide the corresponding Lamellarin.

General Procedure J

To a 0.005M solution of Lamellarin (1 eq.) in methanol, palladium/C 10% (1 eq., w/w) was added and the resulting suspension was stirred at room temperature under hydrogen atmosphere. The mixture was filtered on celite and washed with dichloromethane. Evaporation of the solvent gave the corresponding Lamellarin.

General Procedure K

To a 0.01M suspension of Lamellarin (1 eq.) in anhydrous dichloromethane, the corresponding carboxylic acid (2 eq. per hydroxy group), 1,3-dicyclohexylcarbodiimide (2 eq. per hydroxy group) and dimethyl-aminopyridine (0.2 eq. per hydroxy group) were added. The mixture was stirred under argon atmosphere at room temperature for 6h. The resulting solution was diluted with dichloromethane, washed with water and saturated sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate and the solvent removed under vacuum. The residue was purified by chromatography on silica gel to provide the corresponding Lamellarin.

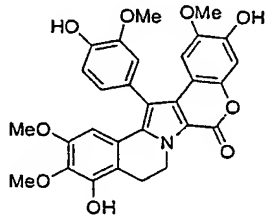
General Procedure L

A 0.01M mixture of the corresponding Lamellarin in acetic anhydride/pyridine (1:2) was stirred overnight at room temperature under argon atmosphere. The solvent was evaporated under reduced pressure to provide the acylated-Lamellarin.

General Procedure M

To a 0.03M solution of **189** (1 eq.) in toluene/ethanol (10:1) under argon atmosphere, the corresponding boronic acid (2 eq.), tetrakis-triphenylphosphine palladium(0) (0.05 eq.) and sodium carbonate 2M (6 eq.) were added. The resulting mixture was heated at 90°C for 16 hours, then water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with sodium hydroxide 1M, water and brine. After drying over sodium sulfate and evaporation of the solvent under reduced pressure, the residue was purified by chromatography on silica gel to provide the corresponding Lamellarin.

Compound **1**



General procedure **A** (starting from **104**) and chromatography on silica gel (CH_2Cl_2:MeOH, from 20:1 to 15:1) to afford **1** (2.27 g, 95%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J= 7.8 Hz, 1H), 7.06 (dd, J= 7.8, 1.7 Hz, 1H), 6.98 (d, J= 1.7 Hz, 1H), 6.93 (s, 1H), 6.59 (s, 1H), 6.38 (s,

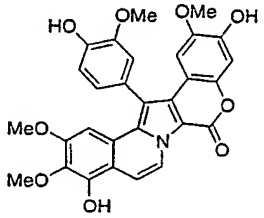
1H), 6.02 (s, 1H), 5.85 (s, 1H), 5.82 (s, 1H), 5.00-4.80 (m, 1H), 4.70-4.50 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.49 (s, 3H), 3.36 (s, 3H), 3.20-3.00 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 150.3, 147.2, 146.3, 146.1, 145.5, 145.4, 143.3, 135.4, 135.3, 128.1, 127.3, 124.2, 123.2, 115.5, 115.1, 113.8, 113.4, 113.0, 110.1, 103.9, 103.3, 101.8, 61.0, 56.2, 55.6, 55.5, 42.0, 21.4.

MS (ESI) m/z: 532 $(M+1)^+$.

Rf: 0.30 (CH_2Cl_2:MeOH, 20:1).

Compound **2**



General procedure **A** (starting from **27**) and chromatography on silica gel (CH_2Cl_2:MeOH, from 20:1 to 10:1) to afford **2** (8 mg, 80%).

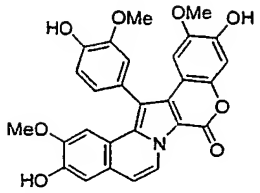
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18 (d, J= 7.5 Hz, 1H), 7.40 (d, J= 7.5 Hz, 1H), 7.20-7.16 (m, 2H), 7.10 (s, 1H), 6.99 (s, 1H), 6.80 (s, 1H), 6.68 (s, 1H), 6.20 (br s, 1H), 5.80 (br s, 2H), 5.80 (br s, 2H), 3.94 (s, 3H), 3.91 (s, 3H), 3.52 (s, 3H), 3.46 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 151.9, 147.3, 147.0, 146.3, 145.7, 144.5, 143.3, 134.8, 133.7, 129.3, 127.5, 124.7, 122.3, 121.4, 119.7, 115.2, 113.9, 113.8, 111.9, 109.8, 106.9, 104.6, 103.5, 98.3, 61.2, 56.3, 55.6, 55.1.

MS (ESI) m/z: 529 $(M+1)^+$.

Rf: 0.30 (CH_2Cl_2:MeOH, 20:1).

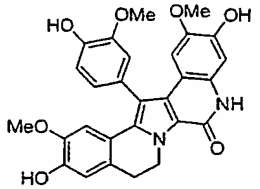
Compound **3**



General procedure **A** (starting from **107**) and chromatography on silica gel (EtOAc, 100%) to afford **3** (92 mg, 43%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.92 (s, 1H), 9.81 (s, 1H), 9.32 (s, 1H), 8.98 (d, J= 7.3 Hz, 1H), 7.22-6.98 (m, 6H), 6.85 (s, 1H), 6.70 (s, 1H), 3.75 (s, 3H), 3.36 (s, 6H).
^{13}C NMR (75 MHz, DMSO-d_6) δ 154.3, 148.7, 148.5, 148.3, 147.8, 146.8, 146.3, 144.6, 134.1, 129.2, 128.9, 125.5, 124.7, 123.9, 117.6, 116.4, 115.1, 113.9, 112.3, 111.5, 110.8, 106.4, 105.7, 105.4, 103.7, 56.0, 55.1, 54.5. MS (APCI) m/z: 500 $(M+1)^+$.
Rf: 0.60 (EtOAc).

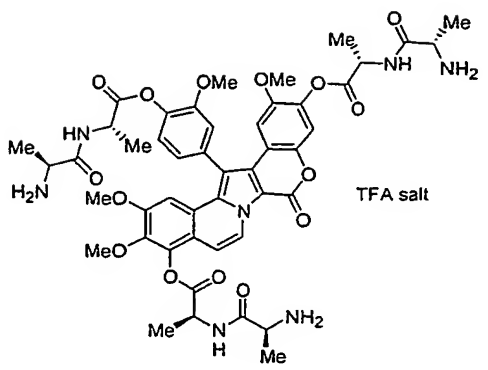
Compound **4**



General procedure **A** (starting from **50**) and chromatography on silica gel (CH_2Cl_2:MeOH, 10:1) to provide **4** (9.1 mg, 76%).

^{1}H NMR (300 MHz, CD_3OD) δ 7.07-7.05 (m, 2H), 6.99-6.97 (m, 1H), 6.80 (br s, 2H), 6.75 (s, 1H), 6.71 (s, 1H), 4.75 (m, 1H), 3.82 (s, 3H), 3.43 (s, 3H), 3.36 (s, 3H), 3.02 (br t, 2H).
MS (ESI) m/z: 501 $(M+1)^+$.
Rf: 0.32 (CH_2Cl_2:MeOH, 10:1).

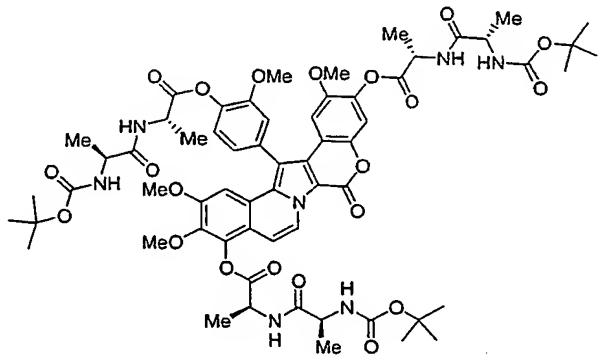
Compound **5**



General procedure **B** (starting from **6**) to afford **5** (30 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 9.07 (br s, 1H), 7.60-7.10 (m, 5H), 6.90-6.60 (m, 2H), 4.85-4.60 (m, 3H), 4.10-3.90 (m, 3H), 3.84 (s, 6H), 3.50 (s, 3H), 3.44 (s, 3H), 1.80-1.50 (m, 18H).
MS (ESI) m/z: 956 $(M+1)^+$.

Compound **6**



General procedure **D** (starting from **2** and Boc-Ala-Ala-OH) and chromatography on silica gel (CH_2Cl_2:MeOH, 20:1) to afford **6** (56 mg, 87%).

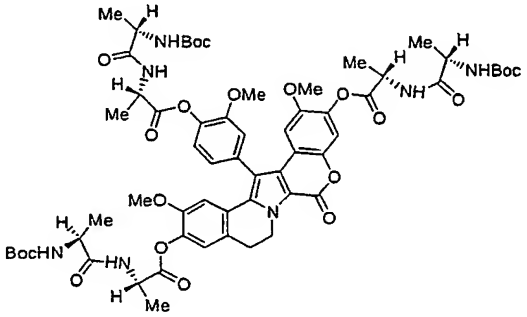
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (br s, 1H), 7.40-7.10 (m, 4H), 7.10-6.90 (m, 3H), 6.90-6.60 (m, 3H), 5.30-5.00 (m, 3H), 5.00-4.75 (m, 3H), 4.26 (br s, 3H), 3.85 (s, 6H), 3.47 (s, 3H), 3.43 (s, 3H), 1.80-1.30 (m, 45H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 172.6, 171.3, 171.2, 171.1, 171.0, 170.9, 155.8, 154.8, 153.4, 153.3, 153.2, 152.4, 152.3, 147.6, 146.8, 145.5, 143.9, 141.8, 140.2, 140.0, 139.5, 138.9, 135.2, 134.8, 133.3, 133.2, 128.3, 128.2, 124.1, 123.8, 123.6, 121.1, 118.4, 115.9, 115.7, 115.5, 112.2, 111.9, 111.4, 109.1, 106.8, 106.4, 106.1, 104.5, 103.7, 80.5, 61.1, 56.6, 55.9, 55.8, 53.6, 50.2, 48.6, 48.4, 48.3, 28.5, 18.6, 18.3.

MS (ESI) m/z: 1279 $(M+23)^+$.

Rf: 0.24 (CH_2Cl_2:MeOH, 20:1).

Compound **7**



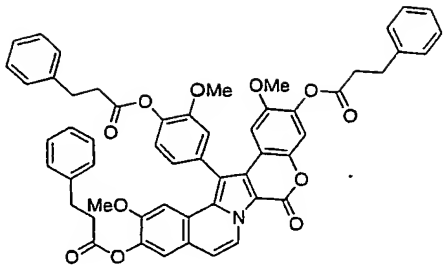
General procedure **D** (starting from **109** and Boc-Ala-Ala-OH) and chromatography on silica gel (CH_2Cl_2:MeOH, 20:1) to afford **7** (46 mg, 75%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.26-6.50 (m, 10H), 5.13-5.11 (m, 3H), 4.87-4.65 (m, 5H), 4.23 (br s, 3H), 3.78 (s, 3H), 3.39 (s, 3H), 3.32 (s, 3H), 3.06 (br t, 2H), 1.63-1.53 (m, 9H), 1.44-1.35 (m, 36H).

MS (ESI) m/z: 1250 $(M+23)^+$.

Rf: 0.40 (CH_2Cl_2:MeOH, 20:1).

Compound **8**



General procedure **E** (starting from **11**, reaction time 21h) and chromatography on silica gel (CH_2Cl_2:MeOH, 100:1) to afford **8** (16 mg, 70%).

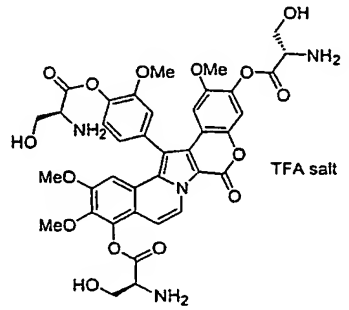
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.23 (d, J= 7.3 Hz, 1H), 7.39-7.20 (m, 20H), 7.08-7.03 (m, 2H), 6.80 (s, 1H), 3.79 (s, 3H), 3.42 (s, 6H), 3.16-3.06 (m, 6H), 3.00-2.90 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 170.7, 170.6, 155.1, 152.4, 151.0, 147.7, 145.4, 140.9, 140.2, 140.1 (2C), 139.7, 134.2, 133.5, 128.5 (6C), 128.4 (2C), 128.4 (4C), 128.2, 126.4, 126.4 (2C), 124.0, 123.8, 123.6, 123.6, 123.1, 120.7, 115.6, 115.0, 112.8, 112.3, 112.1, 109.0, 106.4, 106.1, 56.2, 55.7, 55.6, 35.4 (3C), 30.9, 30.8 (2C).

MS (APCI) m/z: 896 $(M+1)^+$.

Rf: 0.25 (CH_2Cl_2:MeOH, 200:1).

Compound **9**



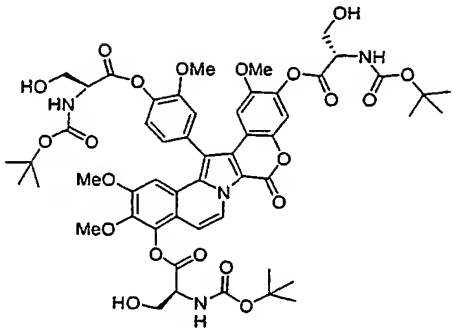
General procedure **B** (starting from **10**) to afford **9** (12 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 9.15 (d, J= 7.5 Hz, 1H), 7.60-7.50 (m, 2H), 7.30-7.35 (m, 2H), 7.29 (s, 1H), 7.23 (s, 1H), 6.89 (s, 1H), 4.73 (br t,

1H), 4.54 (br t, 1H), 4.44 (br t, 1H), 4.30-4.10 (m, 6H), 3.89 (s, 6H), 3.54 (s, 3H), 3.47 (s, 3H).

MS (ESI) m/z: 791 $(M+1)^+$.

Compound **10**



General procedure **E** (starting from **60**, reaction time 22h) and chromatography on silica gel (CH_2Cl_2:MeOH, 20:1) to afford **10** (17 mg, 61%).

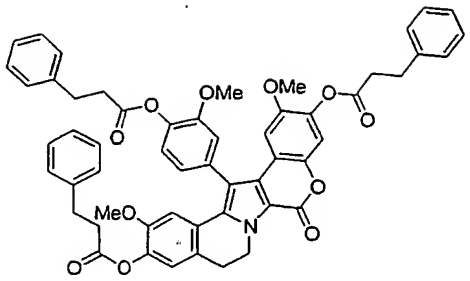
^1H NMR (300 MHz, $CDCl_3$) δ 9.05 (br s, 1H), 7.40-7.00 (m, 6H), 6.72 (d, J= 12.4 Hz, 1H), 5.70 (br s, 1H), 5.55 (br s, 2H), 4.90-4.60 (m, 3H), 4.32 (br s, 2H), 4.20-3.80 (m, 9H), 3.49 (s, 3H), 3.46 (s, 3H), 3.00-2.50 (m, 3H), 1.51 (s, 18H), 1.47 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 169.2, 155.6, 154.5, 153.0, 151.7, 146.8, 145.5, 141.3, 139.8, 139.2, 138.7, 134.7, 133.0, 127.9, 124.0, 123.4, 120.9, 118.2, 115.8, 115.3, 112.1, 111.8, 108.9, 106.9, 106.2, 104.3, 80.6, 64.0, 63.7, 61.1, 56.5, 56.1, 55.8, 55.6, 28.3.

MS (ESI) m/z: 1113 $(M+23)^+$, 1091 $(M+1)^+$.

Rf: 0.30 (CH_2Cl_2:MeOH, 20:1).

Compound **11**



General procedure **F** (starting from **109** and hydrocinnamoyl chloride) and chromatography on silica gel (CH_2Cl_2:MeOH, from 200:1 to 100:1) to afford **11** (31 mg, 69%).

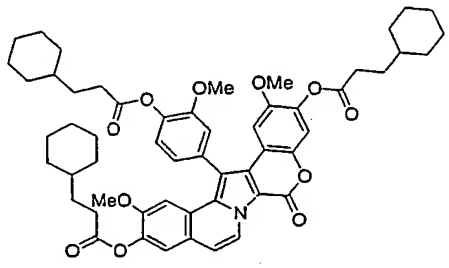
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.21 (m, 15H), 7.13-7.02 (m, 4H), 6.87 (s, 1H), 6.77 (s, 1H), 6.68 (s, 1H), 4.92-4.83 (m, 1H), 4.79-4.70 (m, 1H), 3.76 (s, 3H), 3.39 (s, 3H), 3.32 (s, 3H), 3.13-3.04 (m, 8H), 2.97-2.87 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 170.7, 170.6, 155.1, 152.2, 149.8, 147.7, 144.9, 140.1 (3C), 140.0, 139.4, 138.9, 135.0, 133.9, 128.5 (6C), 128.4 (6C), 127.1, 126.4, 126.4, 126.4, 125.9, 125.6, 123.8, 123.1, 122.6, 116.0, 115.9, 114.9, 114.6, 111.9, 109.7, 105.4, 56.1, 55.7, 55.5, 42.4, 35.5 (3C), 30.9, 30.9, 30.8, 28.0.

MS (ESI) m/z: 898 $(M+1)^+$.

Rf: 0.25 (CH_2Cl_2:MeOH, 200:1).

Compound **12**

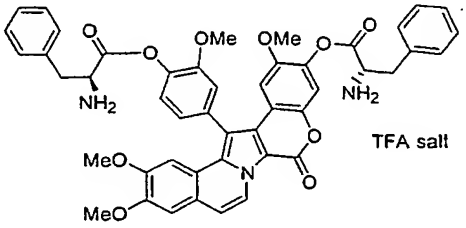


General procedure **E** (starting from **106**, reaction time 17h) and chromatography on silica gel (CH_2Cl_2:MeOH, 50:1) to affrord **12** (21 mg, quant.).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.23 (d, J= 7.3 Hz, 1H), 7.38 (s, 1H), 7.29-7.13 (m, 5H), 7.06 (d, J= 7.5 Hz, 1H), 6.81 (s, 1H), 3.82 (s, 3H), 3.45 (s, 6H), 2.67-2.57 (m, 6H), 1.82 (m, 21H), 1.40-1.13 (m, 12H), 1.04-0.85 (m, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 171.9 (2C), 155.1, 152.5, 151.1, 147.9, 145.5, 141.0, 140.4, 139.9, 134.1, 133.6, 128.3, 124.1, 123.8, 123.6, 123.1, 120.7, 115.6, 115.0, 112.8, 112.3, 112.2, 109.0, 106.4, 106.1, 56.2, 55.8, 55.7, 37.3 (3C), 37.1 (3C), 33.0 (6C), 32.3, 32.3, 32.2, 31.6 (3C), 26.5 (2C), 26.3 (2C), 26.3 (2C).

MS (ESI) m/z: 914 $(M+1)^+$.
Rf: 0.17 (hexane:EtOAc, 4:1).

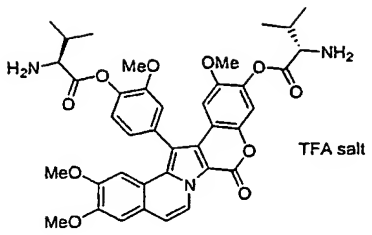
Compound **13**



General procedure **B** (starting from **58**) to afford **13** (10.5 mg, quant).

^{1}H NMR (300 MHz, CD_3OD) δ 8.93 (d, J= 7.1 Hz, 1H), 7.58 (d, J= 7.8 Hz, 1H), 7.47-7.34 (m, 12H), 7.20 (s, 1H), 7.12 (d, J= 7.3 Hz, 1H), 7.08 (s, 1H), 7.05 (d, J= 4.0 Hz, 1H), 6.83 (s, 1H), 4.76 (br t, J= 6.8 Hz, 1H), 4.61 (m, 1H), 3.95 (s, 3H), 3.86 (s, 3H), 3.46-3.31 (m, 7H).
MS (ESI) m/z: 830.1 $(M+23)^+$, 808 $(M+1)^+$.

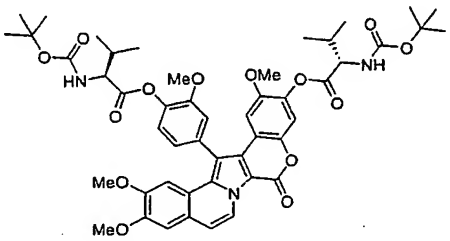
Compound **14**



General procedure **B** (starting from **15**) to afford **14** (11.6 mg, quant).

^{1}H NMR (300 MHz, CD_3OD) δ 9.05 (m, 1H), 7.58-7.47 (m, 2H), 7.38-7.31 (m, 3H), 7.38-7.10 (m, 4H), 6.88 (br d, 1H), 4.36 (m, 1H), 4.25 (m, 2H), 3.92 (s, 3H), 3.88 (s, 3H), 3.47 (s, 6H), 2.50-2.48 (m, 2H), 1.27 (d, J= 6.1 Hz, 6H), 1.20 (d, J= 6.8 Hz, 6H).
MS (ESI) m/z: 712 $(M+1)^+$.

Compound **15**



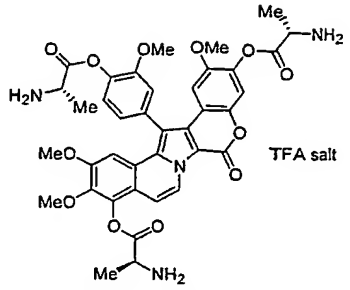
General procedure **E** (starting from **65**, reaction time 20h) and chromatography on silica gel (CH_2Cl_2:MeOH, 60:1) to afford **15** (29.0 mg, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.20 (d, J= 7.6 Hz, 1H), 7.32-7.23 (m, 3H), 7.12-7.05 (m, 4H), 6.80 (d, J= 9.2 Hz, 1H), 5.09 (br d, 2H), 4.52 (br s, 2H), 3.98 (s, 3H), 3.80 (s, 3H), 3.50 (s, 3H), 3.43 (s, 3H), 2.43-2.37 (m, 2H), 1.49 (s, 9H), 1.46 (s, 9H), 1.14-0.99 (m, 12H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 155.7 (2C), 154.9, 152.2, 150.3, 149.6, 147.5, 145.5, 139.9, 139.3, 134.8, 134.2, 128.3, 128.2, 124.7, 123.9 (2C), 123.1, 118.9, 116.0, 115.3, 113.0, 112.1, 110.9, 108.4, 107.4, 106.2, 105.1, 80.0 (2C), 58.6 (2C), 56.0, 55.9, 55.7, 55.6, 31.3, 31.2, 28.3 (9C), 19.2, 19.0, 17.1 (2C).

MS (ESI) m/z: 934.2 $(M+23)^+$, 912 $(M+1)^+$.

Rf: 0.54 (CH_2Cl_2:MeOH, 60:1).

Compound **16**

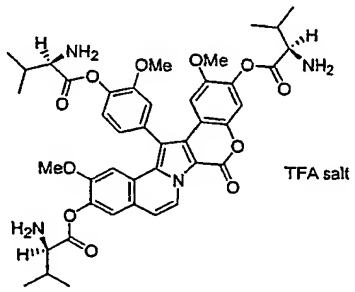


General procedure **B** (starting from **97**) to afford **16** (31 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 9.11 (dd, J= 7.5, 2.3 Hz, 1H), 7.60-7.50 (m, 2H), 7.35 (t, J= 6.6 Hz, 1H), 7.25-7.20 (m, 3H), 6.86 (d, J= 9.5 Hz, 1H), 4.66 (q, J= 7.3 Hz, 1H), 4.52 (q, J= 7.3 Hz, 1H), 4.38 (q, J= 7.1 Hz, 1H), 3.90 (d, J= 3.2 Hz, 3H), 3.89 (d, J= 1.8 Hz, 3H), 3.53 (d, J= 2.7 Hz, 3H), 3.47 (s, 3H), 1.85 (d, J= 7.0 Hz, 3H), 1.80 (d, J= 7.1 Hz, 3H), 1.69 (dd, J= 7.1, 4.0 Hz, 3H).

MS (ESI) m/z: 743 $(M+1)^+$.

Compound **17**

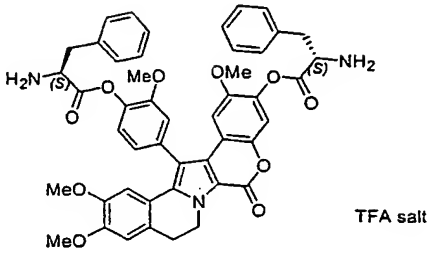


General procedure **B** (starting from **122**) to afford **17** (21 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 9.13-9.09 (m, 1H), 7.63-7.52 (m, 3H), 7.44-7.22 (m, 4H), 6.89 (d, J= 9.2 Hz, 1H), 4.36 (d, J= 4.4 Hz, 1H), 4.32

(d, J= 4.0 Hz, 1H), 4.25 (t, J= 3.8 Hz, 1H), 3.91 (s, 3H), 3.48 (s, 6H), 2.61-2.44 (m, 3H), 1.29-1.19 (m, 18H).
MS (ESI) m/z: 797 $(M+1)^+$.

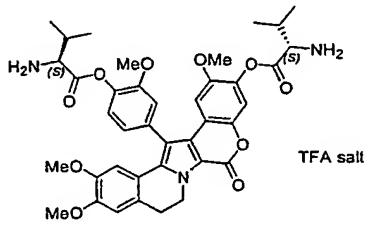
Compound **18**



General procedure **B** (starting from **84**) to afford **18** (21.6 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 7.44-7.37 (m, 11H), 7.23-7.20 (m, 2H), 7.03 (s, 1H), 6.90 (s, 1H), 6.78 (m, 1H), 6.67 (s, 1H), 4.72-4.60 (m, 4H), 3.90 (s, 3H), 3.81 (s, 3H), 3.44 (s, 3H), 3.39-3.30 (m, 4H), 3.11 (br t, 2H).
MS (ESI) m/z: 810 $(M+1)^+$.

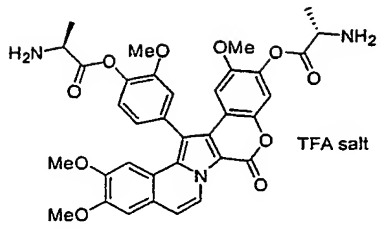
Compound **19**



General procedure **B** (starting from **65**) to afford **19** (43.3 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 7.43-7.40 (m, 2H), 7.25-7.17 (m, 3H), 6.94 (br s, 1H), 6.80 (d, J= 13.4 Hz, 1H), 6.69 (d, J= 9.03 Hz, 1H), 4.90 (m, 2H), 4.32 (m, 1H), 4.22 (m, 2H), 3.86 (s, 3H), 3.45 (s, 3H), 3.36 (s, 3H), 3.13 (br t, 2H), 2.58-2.40 (m, 2H), 1.25 (br d, 6H), 1.17 (br d, 6H).
MS (ESI) m/z: 736 $(M+23)^+$, 714 $(M+1)^+$.

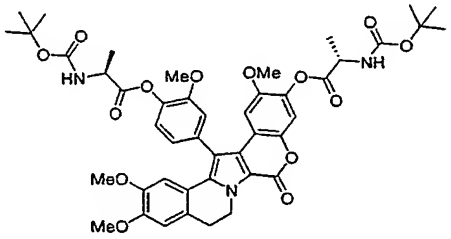
Compound **20**



General procedure **B** (starting from **77**) to afford **20** (11.7 mg, quant).

^{1}H NMR (300 MHz, CD_3OD) δ 9.03 (d, J= 7.3 Hz, 1H), 7.57-7.48 (m, 2H), 7.37-7.32 (m, 1H), 7.26-7.25 (m, 1H), 7.21-7.20 (m, 2H), 7.11 (d, J= 6.8 Hz, 1H), 6.87 (d, J= 8.3 Hz, 1H), 4.52 (br q, J= 6.8 Hz, 1H), 4.42 (br q, J= 6.8 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.48 (s, 6H), 1.85 (d, J= 7.3 Hz, 1H), 1.71 (d, J= 7.1 Hz, 1H).
MS (ESI) m/z: 678 $(M+23)^+$, 656 $(M+1)^+$.

Compound **21**

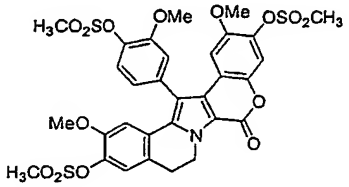


General procedure **D** (starting from **95** and Boc-Ala-OH) and chromatography on silica gel (CH_2Cl_2:MeOH, 60:1) to afford **21** (83.2 mg, 100%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (br s, 1H), 7.16-7.10 (m, 3 H), 6.76 (s, 1H), 6.71-6.56 (m, 2H), 5.10 (m, 1H), 4.92-4.70 (m, 2H), 4.60-4.58 (m, 2H), 3.89 (s, 3H), 3.78 (s, 3H), 3.41 (s, 3H), 3.40 (s, 3H), 3.13 (t, J= 7.1 Hz, 2H), 1.63-1.46 (m, 24H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 154.9, 151.9, 149.1, 147.6, 147.3, 144.8, 139.6, 138.4, 135.8, 134.4, 127.0, 126.4, 123.6, 123.3, 119.5,

116.2, 114.8, 114.6, 114.3, 111.6, 110.9, 108.4, 105.4, 79.9 (2C), 56.1, 55.8, 55.7, 55.3, 49.3 (2C), 42.4, 28.4, 28.2 (6C), 18.5 (2C).
MS (ESI) m/z: 880 $(M+23)^+$, 857 $(M+1)^+$.
Rf: 0.15 (CH_2Cl_2:MeOH, 60:1).

Compound **22**

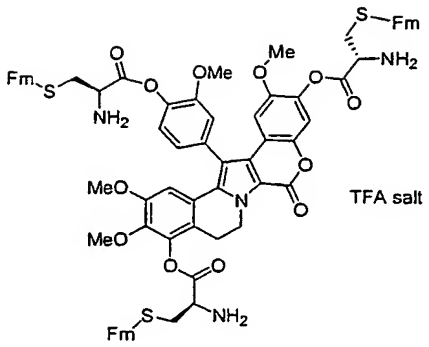


To a suspension of **109** (50 mg, 0.0997 mmol) in anhydrous CH_2Cl_2 (2 mL) under Argon at 0 °C, Et_3N (83 µL, 0.5982 mmol) and methanesulfonyl chloride (47 µL, 0.5982 mmol) were added. The resulting mixture was stirred at 23 °C for 6 h, then quenched with H_2O and extracted with CH_2Cl_2 (3x20 mL).

The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The resulting residue was purified on silica gel (CH_2Cl_2:MeOH, 80:1) to afford **22** as a pale yellow solid (47 mg, 64%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, J= 8.1 Hz, 1H), 7.30 (s, 1H), 7.23-7.20 (m, 2H), 7.17 (d, J= 1.6 Hz, 1H), 6.75 (s, 1H), 6.65 (s, 1H), 4.99-4.90 (m, 1H), 4.71-4.61 (m, 1H), 3.92 (s, 3H), 3.46 (s, 3H), 3.38 (s, 3H), 3.34 (s, 3H), 3.19 (s, 3H), 3.18 (s, 3H), 3.14 (t, J= 6.0 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 152.8, 150.1, 148.0, 144.6, 138.0, 137.7, 136.9, 135.4, 134.4, 126.5, 126.4, 126.3, 125.6, 124.4, 123.3, 117.0, 115.8, 115.4, 115.2, 113.5, 109.9, 105.6.
MS (ESI) m/z: 736 $(M+1)^+$.
Rf: 0.33 (CH_2Cl_2:MeOH, 80:1).

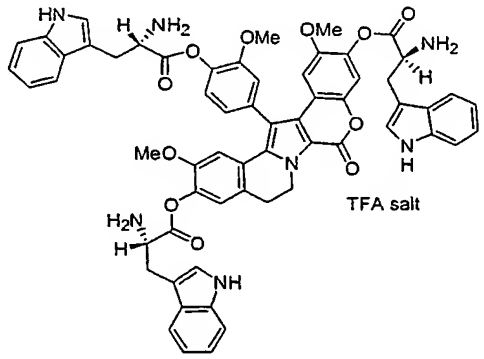
Compound **23**



General procedure **B** (starting from **114**) to give **23** (20 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 7.90-7.60 (m, 12H), 7.45-7.20 (m, 16H), 6.80-6.70 (m, 2H), 4.80-4.40 (m, 5H), 4.35-4.20 (m, 3H), 3.74 (d, J= 2.9 Hz, 3H), 3.71 (d, J= 2.3 Hz, 3H), 3.55-3.30 (m, 12H) 3.35-3.00 (m, 6H), 2.91 (br s, 2H).
MS (ESI) m/z: 1375 $(M)^+$.

Compound **24**

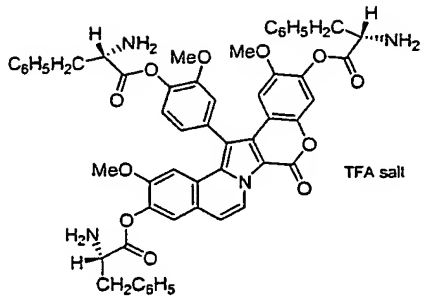


General procedure **B** (starting from **29**) to afford **24** (27 mg, quant.)

^{1}H NMR (300 MHz, CD_3OD) δ 7.68 (d, J= 8.1 Hz, 1H), 7.62 (s, 1H), 7.60 (s, 1H), 7.44 (s, 1H), 7.42 (s, 3H), 7.34 (s, 1H), 7.30 (s, 1H), 7.29 (s, 1H), 7.21-7.16 (m, 5H), 7.12-7.09 (m, 3H), 6.98 (s, 1H), 6.85 (d, J= 2.0 Hz, 1H), 6.77-6.76 (m, 2H), 4.73-4.69 (m, 3H), 4.60 (br t, 2H), 3.87 (s, 3H), 3.77-3.34 (m, 6H), 3.43 (s, 3H), 3.34 (s, 3H).

MS (ESI) m/z: 1060 $(M+1)^+$.

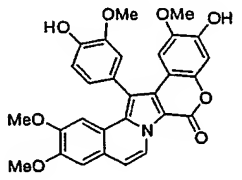
Compound **25**



General procedure **B** (starting from **113**) to afford **25** (20 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 9.08 (d, J= 7.5 Hz, 1H), 7.60 (d, J= 2.2 Hz, 1H), 7.53 (s, 1H), 7.49-7.36 (m, 17H), 7.30 (d, J= 3.5 Hz, 1H), 7.20 (d, J= 7.5 Hz, 1H), 7.08 (d, J= 4.8 Hz, 1H), 6.87 (d, J= 4.2 Hz, 1H), 4.76 (t, J= 7.0 Hz, 1H), 4.70 (t, J= 6.9 Hz, 1H), 4.63 (t, J= 6.2 Hz, 1H), 3.95 (s, 3H), 3.47 (s, 6H), 3.61-3.36 (m, 6H).
MS (ESI) m/z: 941 $(M+1)^+$.

Compound **26**



General procedure **A** (starting from **111**) and chromatography on silica gel (CH_2Cl_2:MeOH, 20:1) to afford **26** (116 mg, 82%).

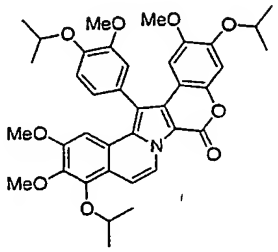
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (d, J= 7.3 Hz, 1H), 7.19-6.98 (m, 7H), 6.71 (s, 1H), 5.86-5.85 (br s, 2H), 3.97 (s, 3H), 3.90 (s, 3H), 3.52 (s, 3H), 3.48 (s, 3H).
^{13}C NMR (75 MHz, DMSO-d_6) δ 154.2, 149.7, 148.7, 148.6, 147.7, 146.8, 146.3, 144.4, 133.5, 128.7, 125.5, 124.2, 124.0, 121.9, 118.2,

116.2, 115.2, 112.2, 110.8, 108.3, 107.7, 106.5, 105.6, 104.8, 103.6, 56.0, 55.4, 55.0, 54.4.

MS (ESI) m/z: 536 $(M+23)^+$, 514 $(M+1)^+$.

Rf: 0.45 (CH_2Cl_2:MeOH, 20:1).

Compound **27**



General procedure **G** (starting from 6,7-dimethoxy-5-isopropoxyisoquinoline) and chromatography on silica gel (hexane:EtOAc, from 3:1 to 2:1) to afford **27** (15 mg, 7%).

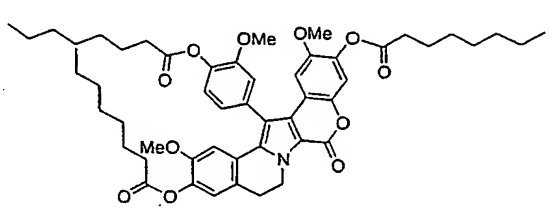
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.20 (d, J= 7.5 Hz, 1H), 7.43 (d, J= 7.6 Hz, 1H), 7.20-7.15 (m, 3H), 7.01 (s, 1H), 6.97 (s, 1H), 6.72 (s, 1H), 4.75-4.50 (m, 3H), 4.65-4.50 (m, 3H), 3.90 (s, 3H), 3.85 (s, 3H), 3.44 (s, 3H), 1.50-1.35 (m, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 155.6, 153.2, 151.4, 147.8, 147.2, 146.6, 146.5, 146.4, 142.5, 133.8, 129.3, 128.7, 123.8, 122.6, 121.3, 120.8, 116.9, 114.9, 111.9, 109.9, 107.7, 105.4, 103.4, 101.4, 76.4, 71.8, 71.4, 60.7, 56.2, 55.4, 55.1, 22.7, 21.9, 21.8.

MS (ESI) m/z: 656 $(M+1)^+$.

Rf: 0.20 (hexane:EtOAc, 2:1).

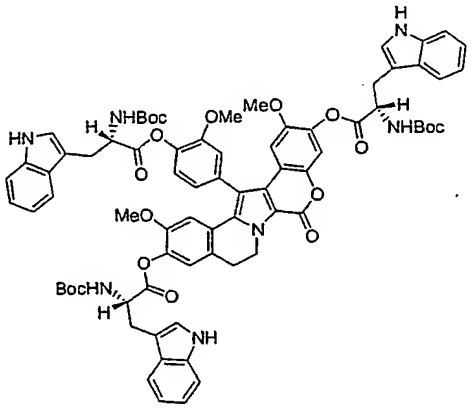
Compound **28**



General procedure **D** (starting from **109** and *n*-octanoic acid) and chromatography on silica gel (CH_2Cl_2:MeOH, 100:1) to afford **28** (42 mg, 95%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.21-7.07 (m, 4H), 6.94 (s, 1H), 6.79 (s, 1H), 6.70 (s, 1H), 4.93-4.84 (m, 1H), 4.79-4.70 (m, 1H), 3.80 (s, 3H), 3.42 (s, 3H), 3.35 (s, 3H), 3.11 (t, J= 6.6 Hz, 2H), 2.63-2.53 (m, 6H), 1.83-1.69 (m, 6H), 1.41-1.30 (m, 24H), 0.93-0.87 (m, 9H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 171.6, 171.5, 155.1, 152.3, 149.9, 147.7, 144.9, 140.1, 139.5, 139.1, 135.1, 133.8, 127.1, 125.9, 125.5, 123.9, 123.1, 122.6, 115.9, 114.9, 114.6, 111.9, 109.7, 105.4, 56.1, 55.7, 55.5, 42.4, 34.0 (3C), 31.7 (3C), 29.0 (2C), 28.9 (4C), 28.0, 25.0 (2C), 24.9, 22.6 (3C), 14.0 (3C).
MS (ESI) m/z: 902 $(M+23)^+$, 880 $(M+1)^+$.
Rf: 0.31 (CH_2Cl_2:MeOH, 100:1).

Compound **29**



General procedure **D** (starting from **109** and Boc-L-Trp-OH) and chromatography on silica gel (CH_2Cl_2:MeOH, from 30:1 to 15:1) to afford **29** (115 mg, 85%).

^1H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.28 (s, 2H), 7.68-7-62 (m, 3H), 7.39-7.36 (m, 3H), 7.26-7.07 (m, 12H), 6.90 (s, 1H), 6.72 (s, 1H),

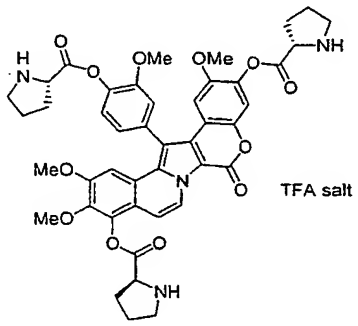
6.65 (br s, 2H), 5.15-5.12 (m, 2H), 5.00-4.59 (m, 6H), 3.75 (s, 3H), 3.52-3.28 (m, 12H), 3.00 (br t, 2H), 1.43 (s, 27H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 170.4, 170.4, 155.3 (2C), 154.9, 152.0, 149.6, 147.5, 144.6, 139.6, 139.0, 138.4, 136.1 (3C), 134.9, 134.0, 127.7 (3C), 126.8, 125.9, 125.5, 123.8, 123.1 (3C), 122.5, 122.0 (3C), 119.5 (3C), 118.6 (3C), 116.0, 115.8, 114.7, 111.7, 111.3 (3C), 109.5 (3C), 105.3, 80.0 (3C), 56.0 (2C), 55.6, 55.4, 54.4 (2C), 42.3, 28.2 (12C), 27.7.

MS (ESI) m/z: 1382 $(M+23)^+$.

Rf: 0.13 (CH_2Cl_2:MeOH, 30:1).

Compound **30**

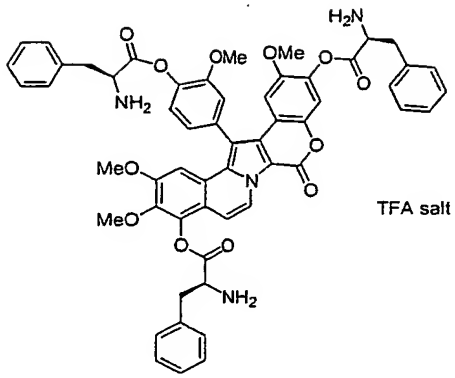


General procedure **B** (starting from **117**) to afford **30** (11 mg, quant.).

^1H NMR (300 MHz, CD_3OD) δ 9.15 (d, J= 7.6 Hz, 1H), 7.65-7.55 (m, 2H), 7.50-7.20 (m, 4H), 6.87 (d, J = 12.3 Hz, 1H), 4.90-4.70 (m, 3H), 3.90 (s, 6H), 3.85-3.40 (m, 12H), 2.90-2.00 (m, 12H).

MS (ESI) m/z: 821 $(M+1)^+$.

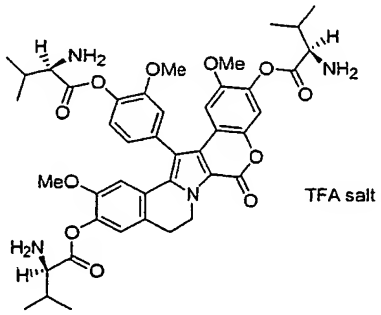
Compound **31**



General procedure **B** (starting from **120**) to afford **31** (31 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 9.09 (d, J= 7.8 Hz, 1H), 7.80-7.40 (m, 18H), 7.30-7.00 (m, 3H), 6.87 (d, J= 5.3 Hz, 1H), 4.80-4.60 (m, 3H), 3.92 (s, 3H), 3.90 (s, 3H), 3.80-3.40 (m, 12H).
MS (ESI) m/z: 971 $(M)^+$.

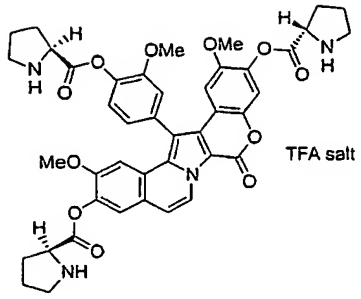
Compound **32**



General procedure **B** (starting from **34**) to afford **32** (19 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 7.46-7.44 (m, 2H), 7.29-7.25 (m, 1H), 7.17-7.14 (m, 2H), 6.90-6.78 (m, 2H), 4.76 (br t, 2H), 4.33-4.21 (m, 3H), 3.88 (s, 3H), 3.45 (s, 3H), 3.38 (s, 3H), 3.16 (br t, 2H), 2.59-2.43 (m, 3H), 1.27-1.10 (m, 18H).
MS (ESI) m/z: 799 $(M+1)^+$.

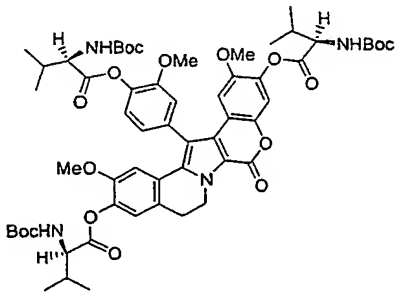
Compound **33**



General procedure **B** (starting from **127**) to afford **33** (19 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 8.96-8.90 (m, 1H), 7.67-7.52 (m, 3H), 7.40-7.24 (m, 2H), 7.13-7.08 (m, 2H), 6.84-6.80 (m, 1H), 4.86-4.67 (m, 3H), 3.95 (s, 3H), 3.55-3.43 (m, 12H), 2.66-2.35 (m, 6H), 2.27-2.14 (m, 6H).
MS (ESI) m/z: 791 $(M+1)^+$.

Compound **34**

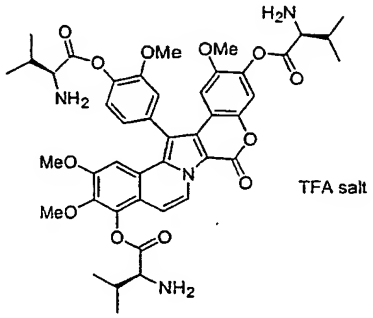


General procedure **D** (starting from **109** and Boc-D-Val-OH) and chromatography on silica gel (CH_2Cl_2:MeOH, 50:1) to afford **34** (100 mg, 91%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.08 (m, 4H), 6.97 (s, 1H), 6.77 (d, J= 7.1 Hz, 1H), 6.69 (d, J= 9.3 Hz, 1H), 5.07-5.05 (m, 3H), 4.96-4.90 (m, 1H), 4.75-4.70 (m, 1H), 4.55-4.47 (m, 3H), 3.78 (s, 3H), 3.40 (s, 3H), 3.33 (s, 3H), 3.21 (br t, 2H), 2.45-2.30 (m, 3H), 1.49 (s, 9H), 1.47 (s, 18H), 1.12-0.99 (m, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 170.3 (2C), 155.6, 154.9, 152.0, 149.7, 147.5, 144.8, 139.6, 139.1, 138.5, 134.9, 134.2, 126.9, 125.9, 125.7, 123.8, 123.1, 122.5, 116.1, 115.8, 114.9, 114.6, 111.8, 109.6, 105.4, 79.9 (3C), 58.5, 55.9, 55.5, 55.5, 55.3, 55.2, 42.3, 31.5, 31.2, 31.1, 28.2 (9C), 27.9, 19.0 (2C), 17.1 (4C).
MS (ESI) m/z: 1099 $(M+1)^+$.
Rf: 0.35 (CH_2Cl_2:MeOH 50:1).

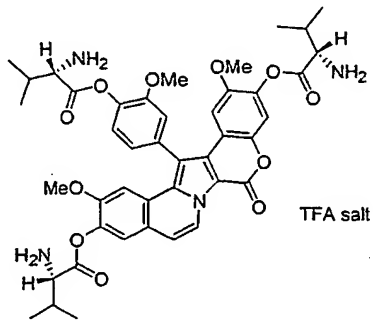
Compound **35**



General procedure **B** (starting from **129**) to afford **35** (13 mg, 98%).

^1H NMR (300 MHz, CD_3OD) δ 9.14 (dd, J= 7.5, 3.0 Hz, 1H), 7.60-7.50 (m, 2H), 7.50-7.20 (m, 4H), 6.87 (d, J= 11.1 Hz, 1H), 4.60-4.50 (m, 1H), 4.40-4.30 (m, 1H), 4.25-4.20 (m, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.52 (s, 3H), 3.47 (s, 3H), 2.80-2.40 (m, 3H), 1.40-1.10 (m, 18H).
MS (ESI) m/z: 827 $(M+1)^+$.

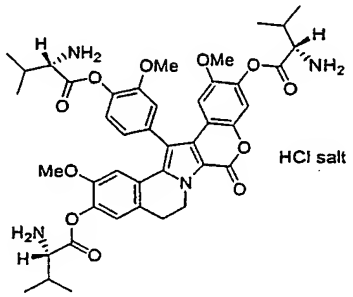
Compound **36**



General procedure **B** (starting from **38**) to afford **36** (21 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 9.09-9.04 (m, 1H), 7.62-7.51 (m, 3H), 7.41-7.32 (m, 2H), 7.23-7.18 (m, 2H), 6.88 (d, J= 9.0 Hz, 1H), 4.36 (d, J= 4.4 Hz, 1H), 4.31 (d, J= 4.4 Hz, 1H), 4.24 (t, J= 4.4 Hz, 1H), 3.92 (s, 3H), 3.48 (s, 6H), 2.62-2.43 (m, 3H), 1.29-1.19 (m, 18H).
MS (APCI) m/z: 797 $(M+1)^+$.

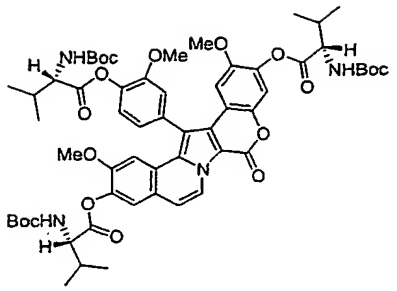
Compound **37**



General procedure **C** (starting from 144) to afford **37** as a white solid (654 mg, 83%).

^{1}H NMR (300 MHz, CD_3OD) δ 7.46-7.43 (m, 2H), 7.26-7.16 (m, 3H), 6.89-6.78 (m, 2H), 4.80 (br t, 2H), 4.33 (s, 1H), 4.24 (s, 2H), 3.84 (s, 3H), 3.45 (s, 3H), 3.37 (s, 3H), 3.18 (br t, 2H), 2.60-2.40 (m, 3H), 1.27-1.17 (m, 18H).
^{13}C NMR (75 MHz, CD_3OD) δ 168.7, 168.3 (2C), 156.2, 153.5, 150.8, 148.8, 146.1, 140.6, 140.0, 139.3, 136.6, 136.4, 128.4, 128.0, 127.5, 125.2, 124.7, 123.7, 117.9, 117.6, 116.5, 116.2, 112.8, 110.9, 106.7, 59.5, 59.4, 56.9, 56.4, 56.2, 56.0, 43.7, 31.3 (3C), 28.8, 18.3 (2C), 18.2 (4C).
MS (ESI) m/z: 799 $(M+1)^+$.

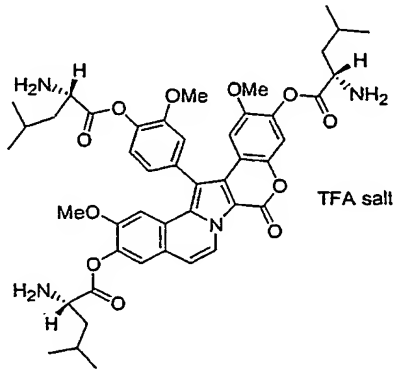
Compound **38**



General procedure **E** (starting from **144**, overnight) and chromatography on silica gel (CH_2Cl_2:MeOH, from 100:1 to 50:1) to afford **38** (43 mg, 88%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.20 (d, J= 7.3 Hz, 1H), 7.40 (s, 1H), 7.30-7.13 (m, 5H), 7.04 (d, J= 7.3 Hz, 1H), 6.79 (d, J= 7.5 Hz, 1H), 5.10-5.06 (m, 3H), 4.56-4.48 (m, 3H), 3.81 (s, 3H), 3.43 (s, 6H), 2.45-2.32 (m, 3H), 1.49 (s, 9H), 1.47 (s, 18H), 1.14-1.00 (m, 18H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4 (3C), 155.7, 155.0, 152.3, 150.9, 147.6, 145.4, 140.6, 140.0, 139.4, 134.5, 133.5, 130.9, 128.8, 128.2, 128.1, 124.1, 123.8, 123.6, 123.2, 120.8, 115.9, 115.1, 112.8, 112.3, 112.2, 109.1, 106.4, 106.2, 80.0 (3C), 58.5, 56.0, 55.6, 55.6, 55.5, 55.5, 31.3 (2C), 31.2, 28.3 (9C), 19.2, 19.1, 17.2 (2C), 17.1 (2C).
MS (ESI) m/z: 1119 $(M+23)^+$, 1097 $(M+1)^+$.
Rf: 0.33 (CH_2Cl_2:MeOH, 100:1).

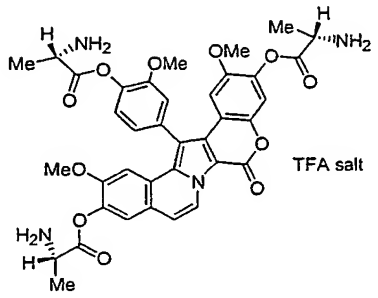
Compound **39**



General procedure **B** (starting from **146**) to afford **39** (19 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 9.15-9.12 (m, 1H), 7.64 (d, J= 2.7 Hz, 1H), 7.58-7.52 (m, 2H), 7.40-7.29 (m, 2H), 7.26-7.22 (m, 2H), 6.89 (d, J= 7.3 Hz, 1H), 4.45-4.31 (m, 3H), 3.90 (s, 3H), 3.48 (s, 3H), 3.48 (s, 3H), 2.11-1.79 (m, 9H), 1.13-1.06 (m, 18H).
MS (ESI) m/z: 839 $(M+1)^+$.

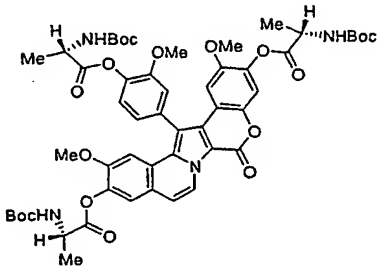
Compound **40**



General procedure **B** (starting from **41**) to afford **40** (16 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 9.03-8.99 (m, 1H), 7.63-7.60 (m, 2H), 7.52 (dd, J= 8.0, 1.6 Hz, 1H), 7.39-7.27 (m, 2H), 7.18-7.15 (m, 2H), 6.85 (d, J= 9.2 Hz, 1H), 4.53-4.36 (m, 3H), 3.93 (s, 3H), 3.48 (s, 6H), 1.80 (d, J= 7.1 Hz, 3H), 1.74 (d, J= 7.3 Hz, 3H), 1.71-1.68 (m, 3H).
MS (ESI) m/z: 713 $(M+1)^+$.

Compound **41**



General procedure **E** (starting from **156**, 2 days) and chromatography on silica gel (hexane:EtOAc, 1:1) to afford **41** (58 mg, 92%).

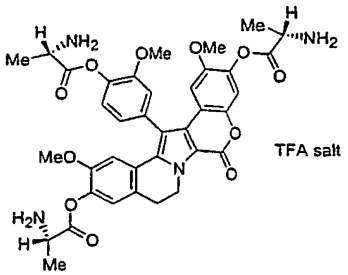
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (d, J= 7.3 Hz, 1H), 7.44-7.32 (m, 2H), 7.25-7.18 (m, 4H), 7.07 (d, J= 7.5 Hz, 1H), 6.79 (d, J= 7.5 Hz, 1H), 5.11-5.09 (m, 3H), 4.64-4.60 (m, 3H), 3.81 (s, 3H), 3.44 (s, 6H), 1.63-1.55 (m, 9H), 1.49 (s, 9H), 1.47 (s, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 171.3, 171.1, 155.0, 154.8, 152.2, 150.8, 147.6, 145.3, 140.6, 140.0, 139.4, 134.4, 133.3, 128.0, 127.9, 123.9, 123.7, 123.7, 123.7, 123.6, 123.0, 120.6, 115.7, 115.1, 112.7, 112.2, 112.0, 108.9, 106.3, 106.1, 80.0 (3C), 56.2 (2C), 55.8, 55.7, 55.7, 55.5, 28.3 (9C), 18.6 (3C).

MS (ESI) m/z: 1035 $(M+23)^+$, 1013 $(M+1)^+$.

Rf: 0.43 (hexane:EtOAc, 50:50).

Compound **42**

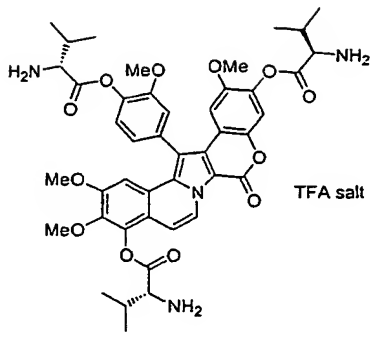


General procedure **B** (starting from **156**) to afford **42** (17 mg, quant.)

^{1}H NMR (300 MHz, CD_3OD) δ 7.46-7.44 (m, 2H), 7.28-7.27 (m, 1H), 7.19 (s, 1H), 7.16 (s, 1H), 6.87 (d, J= 8.8 Hz, 1H), 6.78 (d, J= 10.0 Hz, 1H), 4.75 (t, J= 6.2 Hz, 2H), 4.77-4.37 (m, 3H), 3.87 (s, 3H), 3.45 (s, 3H), 3.38 (s, 3H), 3.16 (t, J= 6.2 Hz, 2H), 1.77 (d, J= 6.9 Hz, 3H), 1.71-1.67 (m, 6H).

MS (ESI) m/z: 715 $(M+1)^+$.

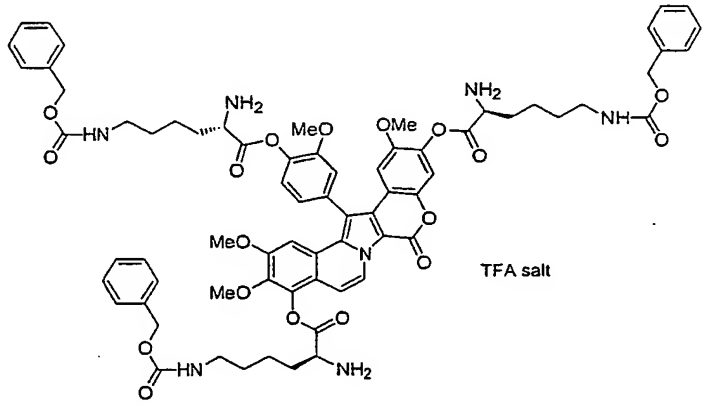
Compound **43**



General procedure **B** (starting from **160**) to afford **43** (13.0 mg, quant.)

^{1}H NMR (300 MHz, CD_3OD) δ 9.18 (d, J= 7.6 Hz, 1H), 7.56-7.52 (m, 2H), 7.40-7.22 (m, 4H), 6.90 (d, J= 10.7 Hz, 1H), 4.60-4.59 (m, 1H), 4.37-4.35 (m, 1H), 4.26-4.24 (m, 1H), 3.90 (br s, 6H), 3.54 (br s, 3H), 3.47 (s, 3H); 2.62-2.47 (s, 3H), 1.32-1.19 (s, 18H).
MS (ESI) m/z: 827 $(M+1)^+$.

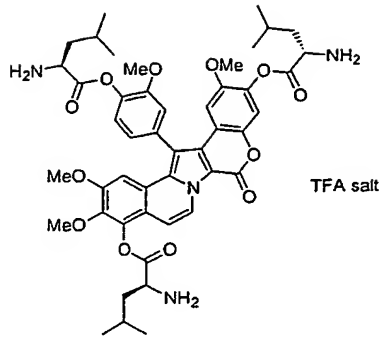
Compound **44**



General procedure **B** (starting from **158**) to afford **44** (12.3 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 9.20 (d, J= 8.1 Hz, 1H); 7.55-7.47 (m, 2H), 7.27-7.18 (m, 19H), 6.87 (d, J= 9.3 Hz, 1H), 5.03 (s, 6H), 4.65 (br t, 1H), 4.49 (br t, 1H), 4.36 (br t, 1H), 3.88 (br s, 3H), 3.85 (br s, 3H), 3.51 (br s, 3H), 3.46 (br s, 3H), 3.22-3.18 (m, 6H), 2.40-2.00 (m, 6H), 1.65-1.50 (m, 12H).
MS (ESI) m/z: 1339 $(M+23)^+$, 1316 $(M+1)^+$.

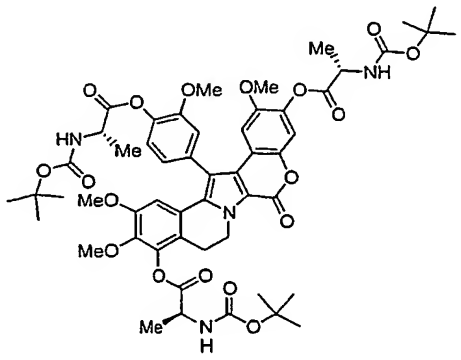
Compound **45**



General procedure **B** (starting from **159**) to afford **45** (27.3 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 9.20 (d, J= 7.6 Hz, 1H), 7.56-7.51 (m, 2H), 7.40-7.22 (m, 4H), 6.89 (d, J= 8.3 Hz, 1H), 4.64 (t, J= 6.0 Hz, 1H), 4.44 (t, J= 6.3 Hz, 1H), 4.34 (t, J= 7.2 Hz, 1H), 3.89 (br s, 6H), 3.54 (br s, 3H), 3.48 (br s, 3H), 2.19-1.79 (m, 9H), 1.15-1.07 (m, 18H).
MS (ESI) m/z: 869 $(M+1)^+$.

Compound **46**



General procedure **D** (starting from **1** and Boc-Ala-OH) and chromatography on silica gel (hexane:EtOAc, 50:50) to afford **46** (80 mg, 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.20 (m, 1H), 7.20-7.05 (m, 3H), 6.67 (d, J= 3.7 Hz, 1H), 6.65 (d, J= 4.0 Hz, 1H), 5.15-5.05 (m, 2H), 4.70-4.50

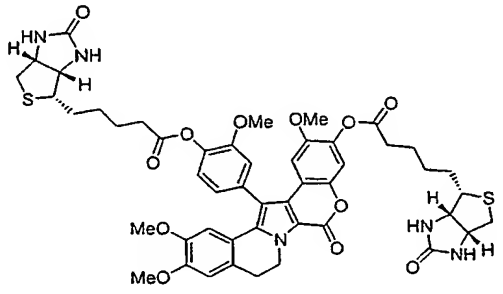
(m, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.40 (s, 3H), 3.38 (s, 3H), 3.01 (br t, 2H), 1.70-1.50 (m, 9H), 1.48 (s, 9H), 1.47 (s, 9H), 1.46 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 171.4, 155.0, 152.1, 151.8, 147.5, 144.9, 144.8, 141.3, 141.0, 139.8, 138.7, 134.8, 134.7, 134.3, 127.1, 127.0, 123.7, 123.2, 122.7, 119.7, 119.4, 116.2, 115.7, 114.9, 114.7, 111.8, 107.6, 105.5, 80.2, 80.1 (2C), 60.8, 56.2, 55.7, 55.5, 49.5, 49.3 (2C), 41.9, 28.3 (9C), 22.1, 18.7, 18.6, 18.3.

MS (ESI) m/z: 1067 $(M+23)^+$, 1045 $(M+1)^+$.

Rf: 0.70 (hexane:EtOAc, 1:2).

Compound **47**



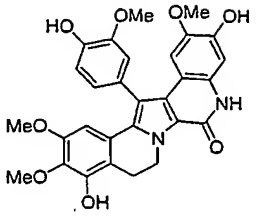
General procedure **D** (starting from **95** and (+)-biotine) and chromatography on silica gel (CH_2Cl_2:MeOH, 10:1) to afford **47** (5 mg, 10%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.10 (m, 4H), 6.80-6.60 (m, 3H), 6.40 (br s, 1H), 6.30 (br s, 1H), 6.20 (br s, 1H), 6.10 (br s, 1H), 4.90-4.70 (m, 2H), 4.60-4.45 (m, 2H), 4.40-4.25 (m, 2H), 3.90 (s, 3H), 3.80 (s, 3H), 3.45 (s, 3H), 3.39 (s, 3H), 3.20-3.10 (m, 4H), 3.00-2.50 (m, 8H), 2.00-1.50 (m, 12H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 171.3, 163.8, 155.2, 152.1, 149.1, 147.6, 144.9, 139.8, 139.0, 135.7, 134.2, 127.4, 126.5, 123.8, 123.5, 123.3, 119.7, 116.0, 114.8, 114.4, 111.8, 111.0, 108.5, 105.4, 62.3, 62.2, 61.4, 60.3, 59.9, 56.2, 56.1, 55.9, 55.8, 55.5, 55.3, 55.2, 42.5, 40.6, 40.5, 33.8, 33.1, 29.7, 28.6, 28.2, 28.1, 27.8, 27.4, 25.1, 24.7, 21.0, 14.2.

MS (ESI) m/z: 990 $(M+23)^+$, 968 $(M+1)^+$.
Rf: 0.20 (CH_2Cl_2:MeOH, 10:1).

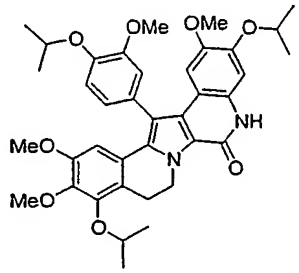
Compound **48**



General procedure **A** (starting from **49**) and purification by chromatography on silica gel (CH_2Cl_2:MeOH, 10:1) to afford **48** (9.9 mg, 84%).

^1H NMR (300 MHz, $CDCl_3$) δ 9.60 (br s, 1H), 7.15-7.07 (m, 2 H), 7.00 (br s, 1H), 6.82 (s, 1H), 6.72 (s, 1H), 6.40 (s, 1H), 6.02 (br s, 1H), 5.80 (br s, 2H), 5.16-5.08 (m, 1H), 4.85-4.78 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.47 (s, 3H), 3.36 (s, 3H), 3.18-3.10 (m, 2H).
MS (ESI) m/z: 531 $(M+1)^+$.
Rf: 0.25 (CH_2Cl_2:MeOH, 10:1).

Compound **49**



General procedure **G** (starting from 6,7-dimethoxy-5-isopropoxy-3,4-dihydroisoquinoline and 2-Bromo-N-[5-isopropoxy-2-(4-isopropoxy-3-methoxy-phenylethynyl)-4-methoxy-phenyl]-acetamide) and purification by chromatography on silica gel (EtOAc:hexane, 4:1) to afford **49** (55.7 mg, 21%).

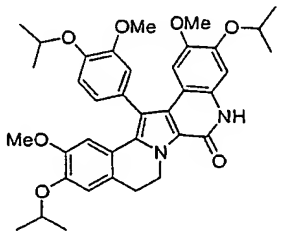
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10-7.08 (m, 3H), 7.00 (s, 1H), 6.77 (s,1H), 6.63 (s, 1H), 4.99 (br t, 2H), 4.63-4.53 (m, 3H), 3.83 (s, 6H), 3.41 (s, 3H), 3.35 (s, 3H), 3.16 (br t, 2H), 1.42 (d, J= 5.4 Hz, 6H), 1.40 (d, 5.4 Hz, 6H), 1.32 (d, 6.1 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 151.7, 151.3, 148.5, 146.8, 145.9, 142.0, 133.3, 129.8, 129.7, 127.3, 123.7, 123.6, 121.0, 118.9, 117.0, 115.4, 114.9, 111.2, 105.3, 104.9, 102.6, 75.7, 71.8, 71.6, 60.5, 56.2, 55.3, 55.1, 42.3, 23.0, 22.7 (2C), 22.0 (2C), 21.9 (2C).

MS (ESI) m/z: 657 $(M+1)^+$.

Rf: 0.34 (EtOAc:hexane, 4:1).

Compound **50**



General procedure **G** (starting from 6-isopropoxy-7-methoxy-3,4-dihydroisoquinoline and 2-Bromo-N-[5-isopropoxy-2-(4-isopropoxy-3-methoxy-phenylethynyl)-4-methoxy-phenyl]-acetamide) and purification by chromatography on silica gel (EtOAc) to provide **50** (51.7 mg, 18%).

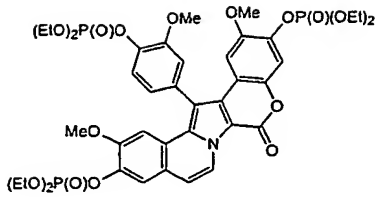
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09-7.08 (m, 3H), 6.95 (br s, 1H), 6.80-6.76 (m, 3H), 5.03-5.00 (m, 2H), 4.62-4.52 (m, 3H), 3.81 (s, 3H), 3.41 (s, 3H), 3.34 (s, 3H), 3.11 (t, J= 6.3 Hz, 2H), 1.42-1.34 (m, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 151.1, 148.4, 146.5, 145.8, 134.0, 129.6, 129.3, 127.4, 126.3, 123.5, 120.7, 118.4, 116.9, 114.7, 114.4, 111.1, 109.0, 105.0, 102.3, 71.8, 71.4, 71.3, 55.9, 55.0, 54.9, 42.3, 28.7, 21.7 (6C).

MS (ESI) m/z: 627 $(M+1)^+$.

Rf: 0.42 (EtOAc).

Compound **51**



General procedure **E** (starting from **52**) and purification by chromatography on silica gel (CH_2Cl_2:MeOH, 20:1) to afford **51** (7 mg, 64%).

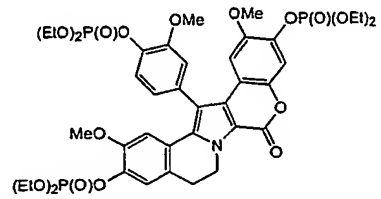
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (d, J= 7.3 Hz, 1H), 7.63 (d, J= 1.2 Hz, 1H), 7.53 (dd, J= 8.0, 1.7 Hz, 1H), 7.37 (d, J= 1.5 Hz, 1H), 7.23-7.15 (m, 3H), 7.08 (d, J= 7.3 Hz, 1H), 6.76 (s, 1H), 4.38-4.22 (m, 12H), 3.88 (s, 3H), 3.48 (s, 3H), 3.47 (s, 3H), 1.45 (t, J= 7.0 Hz, 6H), 1.38 (t, J= 7.0 Hz, 12H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 152.0 (d, J_{C-P}= 4.5 Hz), 150.6 (d, J_{C-P}= 5.5 Hz), 147.4 (d, J_{C-P}= 5.0 Hz), 145.5, 140.9 (d, J_{C-P}= 7.1 Hz), 140.2 (d, J_{C-P}= 7.1 Hz), 139.9 (d, J_{C-P}= 7.1 Hz), 133.5, 133.3, 128.2, 123.9, 123.7, 123.3, 122.8 (d, J_{C-P}= 3.0 Hz), 122.6, 118.8, 115.4, 114.6, 112.8, 111.9, 110.8, 108.9, 106.5, 106.3, 64.9, 64.8 (2C), 64.7 (2C), 64.6, 56.3, 55.8, 55.6, 16.2, 16.1 (3C), 16.0.

MS (ESI) m/z: 908 $(M+1)^+$.

Rf: 0.29 (CH_2Cl_2:MeOH, 20:1).

Compound **52**



To a suspension of **109** (15 mg, 0.030 mmol) in anhydrous CH_2Cl_2 under Argon atmosphere, Et_3N (17 µL, 0.120 mmol) and diethyl

chlorophosphate (18 μL, 0.120 mmol) were added and the mixture was stirred at 23 °C. After 4.5 h, two more equivalents of Et_3N (9 μL, 0.060 mmol) and diethyl chlorophosphate (9 μL, 0.060 mmol) were added and the mixture stirred at 23 °C overnight. The mixture was concentrated under reduced pressure and the residue purified by chromatography on silica gel (CH_2Cl_2:MeOH, from 30:1 to 15:1) to give **52** as a white solid (20 mg, 74%).

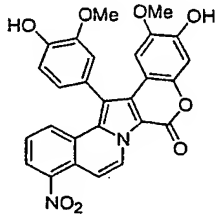
^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, J= 8.1, 1.5 Hz, 1H), 7.29 (d, J=1.5 Hz, 1H), 7.18 (s, 1H), 7.10 (dd, J= 8.1, 1.6 Hz, 1H), 7.06 (s, 1H), 6.71 (s, 1H), 6.64 (s, 1H), 4.94-4.86 (m, 1H), 4.72-4.63 (m, 1H), 4.34-4.18 (m, 12H), 3.84 (s, 3H), 3.44 (s, 3H), 3.36 (s, 3H), 3.09 (br t, 2H), 1.44-1.31 (m, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 151.7 (d, J_{C-P}= 4.5 Hz), 149.3 (d, J_{C-P}= 5.5 Hz), 147.4 (d, J_{C-P}= 5.0 Hz), 144.9, 139.9 (d, J_{C-P}= 7.1 Hz), 139.6 (d, J_{C-P}= 6.5 Hz), 139.1 (d, J_{C-P}= 7.6 Hz), 135.0, 133.0, 127.0, 126.2, 124.4, 123.2, 122.6, 122.6, 121.1, 115.5, 114.9, 114.8, 110.5, 109.8, 105.6, 64.7, 64.7, 64.7 (3C), 64.6, 56.2, 55.8, 55.5, 42.4, 28.1, 16.2, 16.1 (3C), 16.0, 16.0.

MS (ESI) m/z: 910 $(M+1)^+$.

Rf: 0.23 (CH_2Cl_2:MeOH, 30:1).

Compound **53**



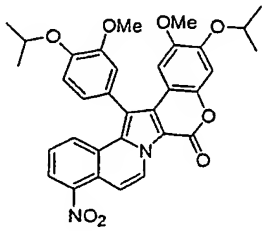
General procedure **A** (starting from **54**) and purification by chromatography on silica gel (CH_2Cl_2:MeOH, from 20:1 to 10:1) to afford **53** (70 mg, 51%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.30 (d, J= 7.6 Hz, 1H), 8.20 (d, J= 7.7 Hz, 1H), 8.08 (d, J= 8.0 Hz, 1H), 7.70-7.50 (m, 2H), 7.20-7.10 (m, 2H), 7.00 (d, J= 7.8 Hz, 1H), 6.88 (s, 1H), 6.57 (s, 1H), 5.69 (s, 1H), 3.76 (s, 3H), 3.40 (s, 3H).

MS (ESI) m/z: 499 $(M+1)^+$.

Rf: 0.61 (CH_2Cl_2:MeOH, 10:1).

Compound **54**



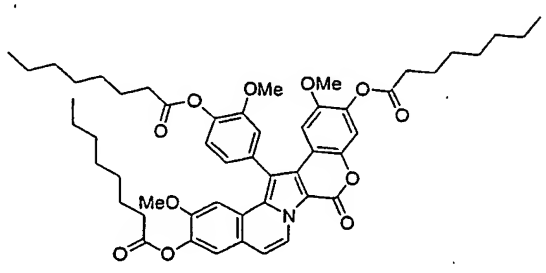
General procedure **H** (starting from 5-nitroisoquinoline) and purification by chromatography on silica gel (hexane:CH_2Cl_2:Et_2O, from 5:5:1 to 5:5:2) to afford **54** (190 mg, 33%).

^{1}H NMR (300 MHz, CD_3OD) δ 9.41 (d, J= 7.8 Hz, 1H), 8.12 (dd, J= 7.8, 1.1 Hz, 1H), 8.06 (dt, J= 8.0, 0.9 Hz, 1H), 7.78 (dd, J= 7.8, 0.7 Hz, 1H), 7.36 (t, J= 8.2 Hz, 1H), 7.19 (d, J= 8.2 Hz, 1H), 7.11 (dd, J= 8.2, 1.8 Hz, 1H), 7.05 (d, J= 1.8 Hz, 1H), 6.96 (s, 1H), 6.63 (s, 1H), 4.71 (hp, J= 6.0 Hz, 1H), 4.58 (hp, J= 6.0 Hz, 1H), 3.84 (s, 3H), 3.44 (s, 3H), 1.51 (d, J= 6.0 Hz, 3H), 1.44 (d, J= 6.0 Hz, 3H), 1.40 (d, J= 7.8 Hz, 6H).

MS (ESI) m/z: 583 $(M+1)^+$.

Rf: 0.50 (hexane:CH_2Cl_2:Et_2O, 5:5:2).

Compound **55**



General procedure **E** (starting from **28**, reaction time 15h) and purification by chromatography on silica gel (CH_2Cl_2:MeOH, 100:1) to afford **55** (17 mg, quant.).

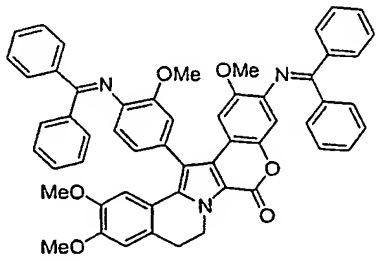
^1H NMR (300 MHz, $CDCl_3$) δ 9.23 (d, J= 7.5 Hz, 1H), 7.38 (s, 1H), 7.30-7.13 (m, 5H), 7.05 (d, J= 7.3 Hz, 1H), 6.81 (s, 1H), 3.82 (s, 3H), 3.45 (s, 6H), 2.65-2.55 (m, 6H), 1.82-1.73 (m, 6H), 1.42-1.25 (m, 24H), 0.91-0.85 (m, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 171.6, 171.6, 155.1, 152.4, 151.1, 147.8, 145.5, 141.0, 140.4, 139.9, 134.1, 133.6, 128.3, 124.1, 123.8, 123.6, 123.6, 123.1, 120.7, 115.6, 115.0, 112.8, 112.3, 112.2, 109.0, 106.4, 106.1, 56.2, 55.8, 55.6, 34.0 (3C), 31.7 (3C), 29.7, 29.0 (2C), 28.9 (3C), 25.0, 25.0, 24.9, 22.6 (3C), 14.1 (3C).

MS (ESI) m/z: 878 $(M+1)^+$.

Rf: 0.31 (CH_2Cl_2:MeOH, 100:1).

Compound **56**

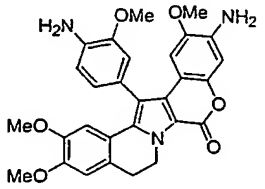


A suspension of **86** (0.2248 g, 0.288 mmol), $Pd(OAc)_2$ (3.8 mg, 0.017 mmol), BINAP (16.2 mg, 0.026 mmol), and Cs_2CO_3 (0.263 g, 0.807 mmol) in anhydrous toluene (5 mL) was stirred at 23 °C under Argon atmosphere for 5 min. Then benzophenone imine (116 mL, 0.692 mmol) was added and the mixture was heated at 110 °C for 3 d. The reaction was cooled to 23 °C, CH_2Cl_2 was added (20 mL), and washed with H_2O (20 mL).

The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was purified by chromatography on silica gel (hexane:EtOAc, 50:50) to give LL-MA-triflate-NPh_2 (56.2 mg, 24%) and **56** (0.102 g, 42%) as a yellow solids.

^1H NMR (300 MHz, $CDCl_3$) δ 7.76-7.70 (m, 4H), 7.48-7.37 (m, 7H), 7.32-7.20 (m, 7H), 7.14-7.10 (m, 2H), 6.98 (dd, J= 7.8, 1.5 Hz, 1H), 6.91 (d, J= 1.5 Hz, 1H), 6.77 (d, J= 7.8 Hz, 1H), 6.74 (s, 1H), 6.71 (s, 1H), 6.60 (s, 1H), 6.59 (s, 1H), 4.89-4.81 (m, 1H), 4.68-4.59 (m, 1H), 3.90 (s, 3H), 3.68 (s, 3H), 3.35 (s, 3H), 3.27 (s, 3H), 3.05 (m, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 169.2, 155.4, 150.1,148.8, 147.4, 146.3, 145.4, 140.9, 140.7, 139.3, 138.9, 136.8, 136.3, 135.6, 130.8, 130.7, 130.6, 129.4, 129.3, 128.7, 128.6, 128.5, 128.4, 128.0, 127.7, 127.6, 126.6, 123.3, 120.9, 119.9, 115.1, 114.0, 113.9, 113.4, 110.8, 109.0, 108.9, 104.6, 55.8, 55.6, 55.5, 55.4, 42.2, 28.6.
MS (ESI) m/z: 842 $(M+1)^+$.
Rf: 0.33 (hexane:EtOAc, 50:50).

Compound **57**



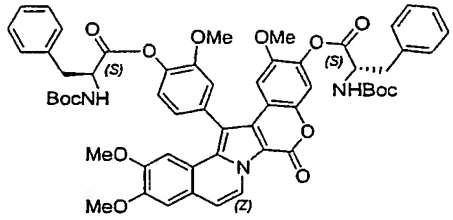
HCl 1.5 N (1.5 mL) was added to a solution of **56** (91.0 mg, 0.108 mmol) in THF (20 mL) at 23 °C. The solution turned from yellow to colorless in 10 min. The solvent was evaporated to dryness and H_2O was added (20 mL).

The suspension was basified with aqueous ammonia 32% (0.5 mL) and extracted with CH_2Cl_2 (3x20 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was evaporated to give a residue which was purified by

chromatography on silica gel (hexane:EtOAc, 1:4) to give **57** as a white solid (55 mg, quant).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95-6.85 (m, 3H), 6.78 (s, 1H), 6.72 (s, 1H), 6.69 (s, 1H), 6.64 (s, 1H), 4.84-4.78 (m, 1H), 4.71-4.65 (m, 1H), 3.98 (br s, 4H), 3.86 (s, 3H), 3.79 (s, 3H), 3.45 (s, 3H), 3.38 (s, 3H), 3.08 (br t, J= 7.3 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 148.6, 147.7, 147.2, 146.6, 143.7, 136.4, 135.8, 135.7, 128.9, 126.4, 124.9, 123.7, 120.3, 115.0, 113.1, 112.9, 110.8, 108.7, 108.3, 103.9, 102.1, 55.8, 55.6, 55.1 (2C), 42.2, 29.2, 28.6.
MS (ESI) m/z: 514 $(M+1)^+$.
Rf: 0.32 (hexane:EtOAc, 1:4).

Compound **58**



General procedure **E** (starting from **84**, reaction time 20h) and purification by chromatography on silica gel (CH_2Cl_2:MeOH, 60:1) to give **58** (30.7 mg, 96%).

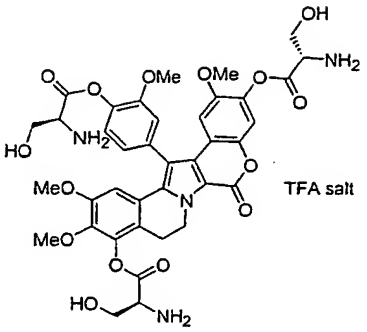
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (d, J= 7.3 Hz, 1H), 7.39-7.25 (m, 11H), 7.10-7.05 (m, 6H), 6.82 (d, J= 7.3 Hz, 1H), 5.03 (m, 2H), 4.91 (m, 2H), 3.99 (s, 3H), 3.84 (s, 3H), 3.49 (s, 3H), 3.44 (s, 3H), 3.37-3.23 (m, 4H), 1.45 (s, 9H), 1.42 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 154.9, 152.1, 150.3, 149.5, 147.5, 145.4, 139.8, 139.2, 135.7 (2C), 134.8, 134.2 (2C), 129.5, 128.6, 128.1 (2C), 124.7, 123.8, 123.0, 119.0, 116.0, 115.4, 113.0, 112.0, 110.8,

108.4, 107.4, 106.2, 105.1, 80.1 (2C), 56.1, 55.9, 55.6 (2C), 54.4 (2C), 38.1 (2C), 28.2 (6C).

MS (ESI) m/z: 1008 $(M+1)^+$.

Rf: 0.60 (CH_2Cl_2:MeOH, 60:1).

Compound **59**

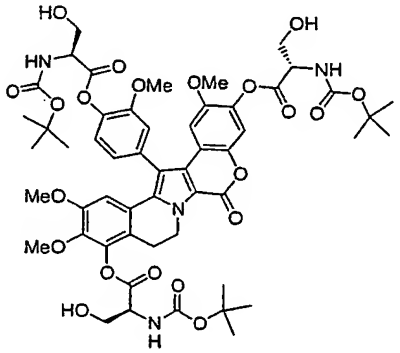


General procedure **B** (starting from **60**) to afford **59** (15 mg, quant.).

^1H NMR (300 MHz, CD_3OD) δ 7.50-7.35 (m, 2H), 7.30-7.20 (m, 2H), 6.85-6.75 (m, 2H), 4.80-4.65 (m, 2H), 4.60 (br s, 1H), 4.53 (t, J= 3.8 Hz, 1H), 4.42 (br t, 1H), 4.30-4.05 (m, 6H), 3.87 (s, 3H), 3.79 (s, 3H), 3.43 (s, 3H), 3.42 (s, 3H), 3.06 (br s, 2H).

MS (ESI) m/z: 793 $(M+1)^+$.

Compound **60**



General procedure **J** (starting from **68**, overnight) and purification by chromatography on silica gel (CH_2Cl_2:MeOH, 10:1) to afford **60** (23 mg, 82%).

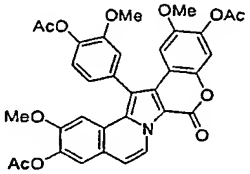
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.00 (m, 4H), 6.75-6.60 (m, 2H), 5.70-5.40 (m, 3H), 4.90-4.50 (m, 4H), 4.40-4.20 (m, 3H), 4.10-3.80 (m, 10H), 3.43 (s, 3H), 3.39 (s, 3H), 3.00 (br s, 2H), 2.80-2.50 (m, 3H), 1.49 (s, 9H), 1.46 (s, 9H), 1.45 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 169.1, 155.6, 154.7, 151.5, 151.4, 147.4, 146.7, 146.4, 145.7, 145.1, 143.5, 141.1, 140.4, 139.6, 139.4, 138.4, 135.0, 134.7, 134.6, 126.9, 126.7, 126.5, 123.9, 123.8, 123.7, 122.9, 119.5, 116.3, 115.6, 114.9, 114.8, 114.3, 113.1, 112.1, 109.7, 107.8, 105.5, 103.5, 80.5, 64.0, 63.7, 61.0, 56.5, 56.3, 56.1, 55.8, 55.6, 55.5, 55.3, 41.9, 28.3, 22.1.

MS (ESI) m/z: 1115 $(M+23)^+$, 1093 $(M+1)^+$.

Rf: 0.45 (CH_2Cl_2:MeOH, 10:1).

Compound **61**



General procedure **E** (starting from **108**, reaction time 24h) and purification by chromatography on silica gel (CH_2Cl_2:MeOH, 40:1) to afford **61** (12 mg, 60%).

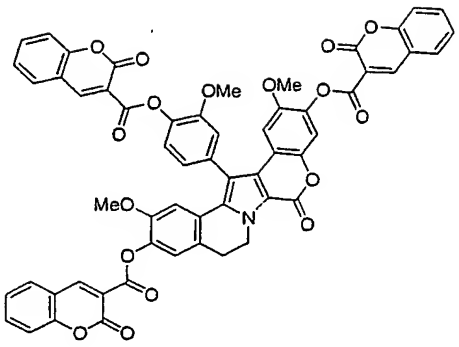
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (d, J= 7.3 Hz, 1H), 7.39 (s, 1H), 7.30 (d, J= 7.7 Hz, 1H), 7.25-7.22 (m, 3H), 7.14 (s, 1H), 7.05 (d, J= 7.5 Hz, 1H), 6.81 (s, 1H), 3.84 (s, 3H), 3.45 (s, 6H), 2.37 (s, 3H), 2.34 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 168.7, 168.7, 155.0, 152.4, 151.0, 147.8, 145.4, 140.9, 140.3, 139.7, 134.2, 133.5, 128.2, 124.1, 123.8, 123.7, 123.6, 123.1, 120.7, 115.7, 115.0, 112.8, 112.3, 112.2, 109.1, 106.4, 106.1, 56.2, 55.7, 55.6, 20.6 (3C).

MS (ESI) m/z: 626 $(M+1)^+$.

Rf: 0.40 (CH_2Cl_2:MeOH, 100:1).

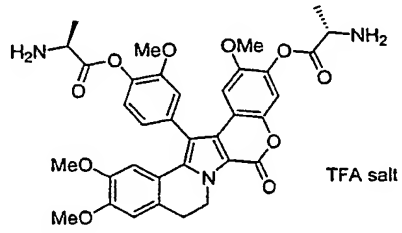
Compound **62**



General procedure **D** (starting from **109** and coumarin 3-carboxylic acid) and purification by chromatography on silica gel (CH_2Cl_2:MeOH, from 50:1 to 40:1) to afford **62** (41 mg, 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.79 (s, 1H), 8.75 (s, 1H), 7.72-7.65 (m, 6H), 7.42-7.34 (m, 7H), 7.26-7.21 (m, 3H), 7.23 (s, 1H), 6.85 (s, 1H), 6.81 (s, 1H), 4.93-4.86 (m, 1H), 4.78-4.69 (m, 1H), 3.84 (s, 3H), 3.50 (s, 3H), 3.44 (s, 3H), 3.15 (br t, 2H).
MS (ESI) m/z: 1040 $(M+23)^+$.
Rf: 0.24 (CH_2Cl_2:MeOH, 50:1).

Compound **63**

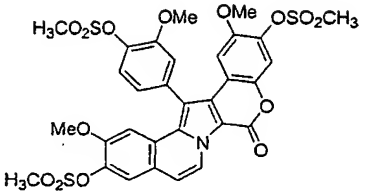


General procedure **B** (starting from **21**) to afford **63** (31.9 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 7.44-7.38 (m, 2H), 7.24-7.20 (m, 2H), 6.94 (br s, 1H), 6.82-6.78 (m, 1H), 6.71-6.68 (m, 1H), 4.72 (m, 1H), 4.49-4.38

(m, 2H), 3.44 (s, 3H), 3.35 (s, 6H), 3.30 (s, 3H), 3.13 (br t, 2H), 1.77 (br d, 3H), 1.70 (br d, 3H).
MS (ESI) m/z: 658 $(M+1)^+$.

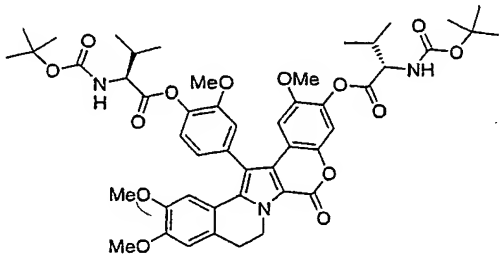
Compound **64**



General procedure **E** (starting from **22**, reaction time 77h) and purification by chromatography on silica gel (CH_2Cl_2:MeOH, 80:1) to afford **64** (17 mg, 68%).

^1H NMR (300 MHz, $CDCl_3$) δ 9.16 (d, J= 7.5 Hz, 1H), 7.66 (s, 1H), 7.60 (d, J= 8.6 Hz, 1H), 7.33-7.30 (m, 3H), 7.18 (s, 1H), 7.06 (d, J= 7.7 Hz, 1H), 6.76 (s, 1H), 3.96 (s, 3H), 3.49 (s, 6H), 3.37 (s, 3H), 3.24 (s, 3H), 3.21 (s, 3H).
MS (APCI) m/z: 734 $(M+1)^+$.
Rf: 0.33 (CH_2Cl_2:MeOH, 80:1).

Compound **65**



General procedure **D** (starting from **95** and (L)-N-Boc-valine) and purification by chromatography on silica gel (CH_2Cl_2:MeOH, 60:1) to afford **65** (83.6 mg, 94%).

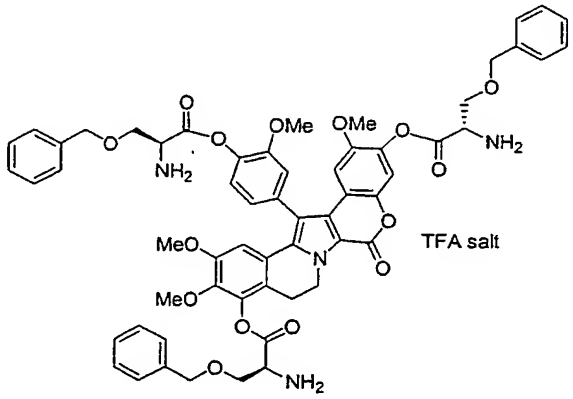
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.09 (m, 4H), 6.76 (br s, 1H), 6.71-6.66 (m, 2H), 5.06 (br d, J= 9.3 Hz, 1H), 4.91-4.71 (m, 2H), 4.53-4.50 (m, 2H), 3.89 (s, 3H), 3.77 (s, 3H), 3.40 (s, 6H), 3.13 (t, J= 7.3 Hz, 2H), 2.41-2.37 (m, 2H), 1.47 (d, J= 6.1 Hz, 18H), 1.12-0.99 (m, 12H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 155.6 (2C), 154.9, 151.9, 149.1, 147.6, 147.4, 144.8, 139.5, 138.4, 135.7, 134.4, 127.1, 127.0, 126.4, 123.7, 123.3, 119.5, 116.2, 114.8, 114.6, 114.4, 111.7, 110.9, 108.5, 105.4, 79.9 (2C), 58.5 (2C), 55.9, 55.8, 55.5, 55.4, 42.4, 31.2, 31.1, 28.5, 28.2 (6C), 19.1, 18.9, 17.1, 17.0.

MS (ESI) m/z: 936 $(M+23)^+$, 914 $(M+1)^+$.

Rf: 0.22 (CH_2Cl_2:MeOH, 60:1).

Compound **66**

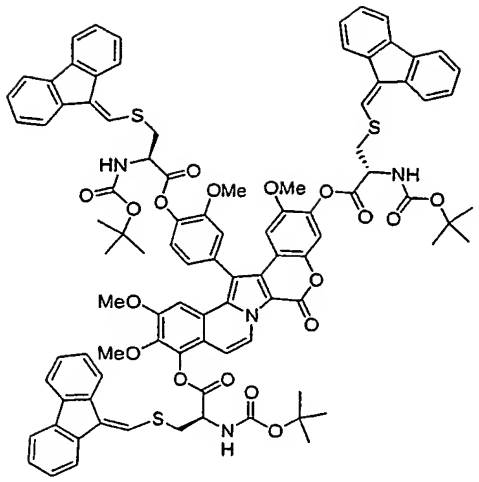


General procedure **B** (starting from **68**) to afford **66** (18 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 7.50-7.20 (m, 17H), 7.16-7.12 (m, 2H), 6.80-6.75 (m, 2H), 4.80-4.60 (m, 11H), 4.35-3.95 (m, 6H), 3.78 (s, 3H), 3.76 (s, 3H), 3.39 (d, J= 2.1 Hz, 3H), 3.36 (d, J= 2.1 Hz, 3H), 2.91 (br s, 2H).

MS (ESI) m/z: 1063 $(M)^+$.

Compound **67**



General procedure **E** (starting from **114**, reaction time 70h) and purification by chromatography on silica gel (hexane:EtOAc, 1:1) to afford **67** (52 mg, 81%).

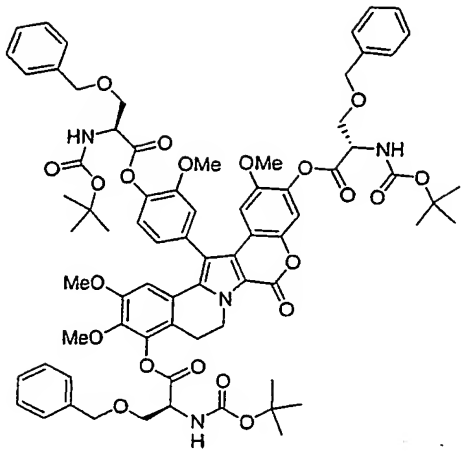
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.06 (d, J= 7.5 Hz, 1H), 8.10-8.00 (m, 3H), 7.80-7.65 (m, 6H), 7.60-7.50 (m, 3H), 7.50-7.10 (m, 21H), 6.74 (s, 1H), 5.80-5.50 (m, 3H), 5.20-5.00 (m, 3H), 3.91 (s, 3H), 3.81 (s, 3H), 3.80-3.60 (m, 6H), 3.50-3.40 (m, 6H), 1.49 (s, 18H), 1.45 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 168.4, 168.3, 168.2, 155.1, 154.9, 154.6, 153.1, 153.0, 152.0, 147.3, 145.3, 141.5, 140.2, 140.1, 140.0, 139.6, 139.0, 138.5, 138.1, 138.0, 136.7, 134.8, 132.9, 132.7, 132.5, 128.0, 127.9, 127.8, 127.7, 127.5, 127.3, 127.2, 127.1, 127.0, 126.9, 126.8, 126.7, 125.9, 125.3, 125.2, 123.8, 123.6, 123.5, 120.8, 119.9, 119.8, 119.7, 119.4, 119.2, 119.1, 117.9, 116.0, 115.1, 112.0, 111.9, 109.0, 106.6, 106.1, 104.4, 80.9, 80.8, 80.7, 61.0, 56.2, 55.8, 55.7, 55.6, 54.3, 54.1, 38.8, 29.7, 28.3, 28.2, 27.3.

MS (ESI) m/z: 1689 $(M+23)^+$.

Rf: 0.19 (hexane:EtOAc, 2:1).

Compound **68**



General procedure **D** (starting from **1** and (L)-N-Boc-Ser(Bzl))and purification by chromatography on silica gel (hexane:EtOAc, 50:50) to afford **68** (153 mg, quant.).

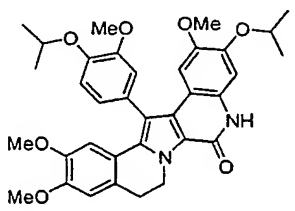
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.25 (m, 15H), 7.20-7.05 (m, 4H), 6.70-6.65 (m, 2H), 5.60-5.45 (m, 3H), 4.80-4.50 (m, 11H), 4.20-4.00 (m, 3H), 3.90-3.80 (m, 3H), 3.74 (s, 6H), 3.36 (t, J= 4.7 Hz, 6H), 2.89 (br s, 2H), 1.48 (s, 18H), 1.46 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 168.8, 155.4, 155.3, 154.9, 152.1, 151.8, 147.5, 144.8, 141.3, 141.1, 139.7, 138.6, 137.4, 137.0, 134.7, 134.3, 128.6, 128.5, 128.4, 128.2, 127.8, 127.6, 127.5, 126.9, 123.8, 123.1, 122.8, 119.4, 116.1, 115.6, 114.7, 111.8, 107.6, 105.5, 80.2, 80.1, 80.0, 73.7, 73.4, 70.0, 69.9, 60.8, 60.3, 56.1, 55.7, 55.5, 54.2, 54.1, 54.0, 41.8, 28.2, 22.0.

MS (ESI) m/z: 1385 $(M+23)^+$.

Rf: 0.59 (hexane:EtOAc, 50:50).

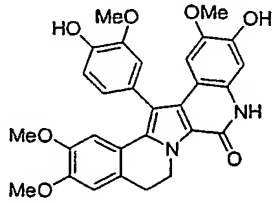
Compound **69**



General procedure **G** (starting from 6,7-dimethoxy-3,4-dihydroisoquinoline and 2-bromo-N-[5-isopropoxy-2-(4-isopropoxy-3-methoxy-phenylethynyl)-4-methoxy-phenyl]-acetamide) and purification by chromatography on silica gel (EtOAc) to afford **69** (4.2 mg, 9%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (br s, 1H), 7.10 (br s, 2H), 7.07 (s, 1H), 6.81 (s, 1H), 6.78 (s, 1H), 6.76 (m, 2H), 5.03-4.94 (m, 2H), 4.61-4.55 (m, 2H), 3.89 (s, 3H), 3.82 (s, 3H), 3.41 (s, 3H), 3.37 (s, 3H), 3.12 (t, J= 6.8 Hz, 2H), 1.40 (d, J= 5.9 Hz, 12H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 151.2, 148.3, 147.3, 146.6, 145.8, 133.6, 129.7, 127.3, 126.3, 123.5, 120.7, 118.6, 116.9, 114.8, 114.5, 111.1, 110.9, 108.5, 105.1, 102.5, 71.7, 71.4, 56.0, 55.8, 55.1, 55.0, 42.3, 29.0, 21.9 (2C), 20.9 (2C).
MS (ESI) m/z: 599 $(M+1)^+$.
Rf: 0.21 (EtOAc).

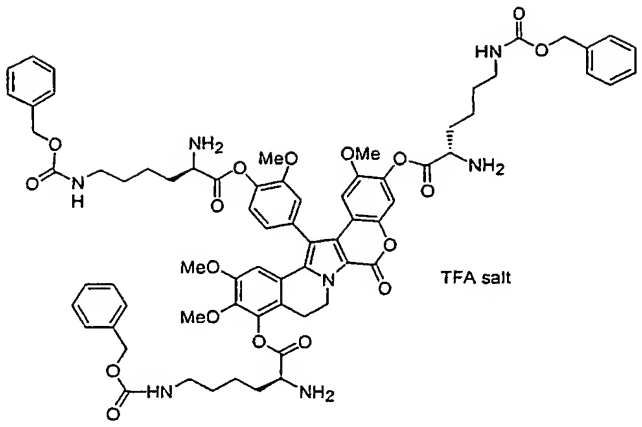
Compound **70**



General procedure **A** (starting from **69**) and purification by chromatography on silica gel (EtOAc) to afford **70** (2.4 mg, 94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (br s, 1H), 7.12-7.07 (m, 2H), 7.00 (s, 1H), 6.79-6.73 (m, 4H), 5.75 (s, 2H), 5.15-5.11 (m, 1H), 4.81 (m, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.49 (s, 3H), 3.39 (s, 3H), 3.13-3.11 (m, 2H).
MS (ESI) m/z: 515 $(M+1)^+$.
Rf: 0.41 (CH_2Cl_2:MeOH, 10:1).

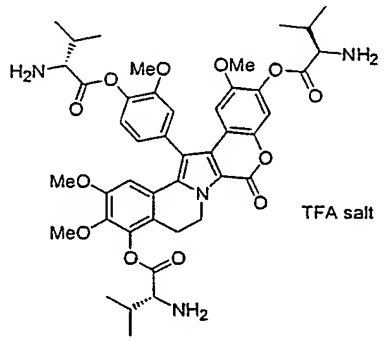
Compound **71**



General procedure **B** (starting from **74**) to afford **71** (14.0 mg, quant.)

^{1}H NMR (300 MHz, CD_3OD) δ 7.45-7.22 (m, 19H), 6.80-6.74 (m, 2H), 5.08 (m, 1H), 5.03 (s, 6H), 4.78 (m, 1H), 4.51 (br t, 1H), 4.42 (br t, 1H), 4.35 (br t, 1H), 3.79 (s, 6H), 3.42 (s, 3H), 3.41 (s, 3H), 3.21 (br s, 6H), 3.05 (m, 2H), 2.15 (m, 6H), 1.65 (m, 12H).
MS (ESI) m/z: 1340 $(M+23)^+$, 1318 $(M+1)^+$.

Compound **72**

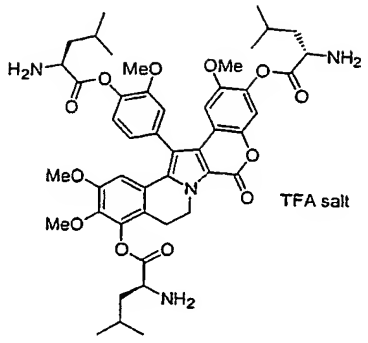


General procedure **B** (starting from **75**) to afford **72** (14.1 mg, quant.)

^{1}H NMR (300 MHz, CD_3OD) δ 7.48-7.42 (m, 2H), 7.28-7.20 (m, 2H), 6.83-6.77 (m, 2H), 4.76 (m, 2H), 4.45 (dd, J= 4.4, 2.0 Hz, 1H), 4.33 (dd, J= 4.4, 2.0 Hz, 1H), 4.23 (dd, J= 4.4, 2.0 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.44 (s, 3H), 3.43 (s, 3H), 3.05 (m, 2H), 2.59-2.44 (m, 3H), 1.38-1.20 (m, 18H).
MS (ESI) m/z: 829 $(M+1)^+$.

Rf: 0.28 (CH_2Cl_2:MeOH, 10:1).

Compound **73**



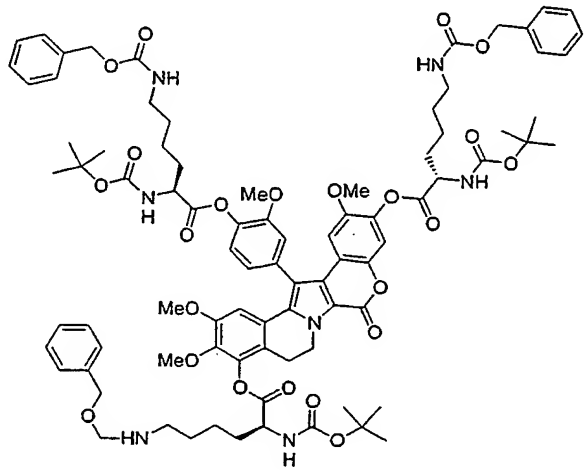
General procedure **B** (starting from **76**) to afford **73** (13.8 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 7.47-7.41 (m, 2H), 7.31-7.21 (m, 2H), 6.81-6.77 (m, 2H), 4.90-4.76 (m, 2H), 4.48 (t, J= 7.3 Hz, 1H), 4.40 (t, J= 7.1 Hz, 1H), 4.42 (t, J= 6.6 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.44 (s, 3H), 3.42 (s, 3H), 3.17-3.06 (m, 2H), 2.14-1.77 (m, 9H), 1.12-1.00 (m, 18H).

MS (ESI) m/z: 871 $(M+1)^+$.

Rf: 0.30 (CH_2Cl_2:MeOH, 10:1).

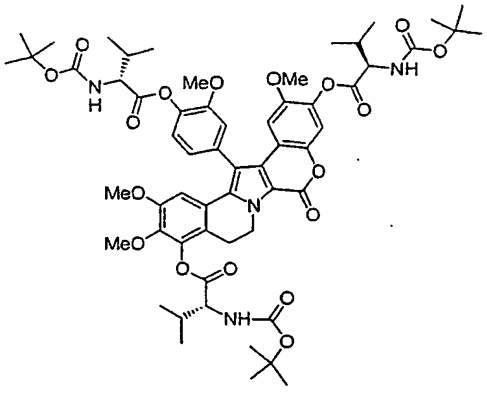
Compound **74**



General procedure **D** (starting from **1** and (L)-N-Boc-Lysine-CBz) and purification by chromatography on silica gel (hexane:EtOAc, 2:3) to afford **74** (114.6 mg, 75%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 -7.31 (m, 15H), 7.15-7.07 (m, 4H), 6.67-6.63 (m, 2H), 5.08 (br s, 6H), 4.92 (m, 3H), 4.55 (m, 2H), 3.77 (s, 6H), 3.39 (s, 3H), 3.37 (s, 3H), 3.26-3.17 (m, 6H), 3.00 (br t, 2H), 2.04-1.76 (m, 6H), 1.58-1.29 (m, 38H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 170.7 (2C), 156.5, 156.4, 155.5, 155.3 (2C), 154.8, 152.0, 151.7, 147.4 (2C), 144.8, 144.7, 141.2 (2C), 140.9 (2C), 139.6, 138.4 (2C), 136.5, 136.4, 134.7, 134.6, 134.2, 128.4, 128.0, 126.9, 126.8, 123.7, 123.2, 122.6, 119.4 (2C), 116.0, 115.6, 114.7(2C), 111.7, 110.8, 105.4 (2C).
MS (ESI) m/z: 1640 $(M+23)^+$.
Rf: 0.30 (hexane:EtOAc, 2:3).

Compound **75**



General procedure **D** (starting from **1** and (D)-N-Boc-Valine) and purification by chromatography on silica gel (hexane:EtOAc, 2:1) to afford **75** (96.5 mg, 91%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.17-7.15 (m, 1H), 7.10-7.09 (m, 2H), 6.69-6.40 (m, 2H), 5.05 (br t, J= 8.1 Hz, 2H), 4.53-4.51 (m, 3H),

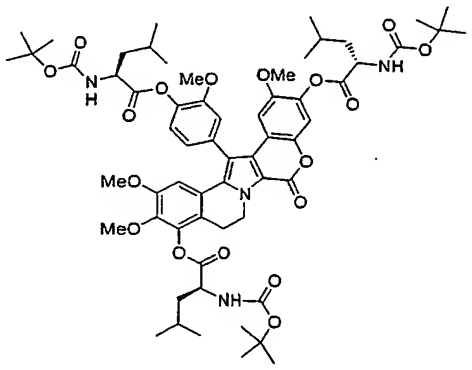
3.78 (s, 6H), 3.40 (s, 3H), 3.38 (s, 3H), 3.01 (br t, 2H), 2.40-2.38 (m, 3H), 1.49 (br s, 27H), 1.15-0.99 (m, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 170.3, 155.7, 155.6 (2C), 154.9, 152.0, 151.8, 147.5, 144.8, 141.2, 141.0, 139.6, 138.5, 134.8, 134.3, 127.0, 126.9, 123.8, 123.2, 122.6, 119.4, 116.1, 115.6, 114.8, 114.7, 111.8, 107.6, 105.4, 80.1, 79.9 (2C), 58.9, 58.5 (2C), 56.0 (2C), 55.5 (2C), 41.8, 31.2, 31.1, 30.8, 28.2 (9C), 22.2, 19.2, 19.1, 18.9, 17.4, 17.1, 17.0.

MS (ESI) m/z: 1129 $(M+1)^+$.

Rf: 0.23 (hexane:EtOAc, 2:1).

Compound **76**



General procedure **D** (starting from **1** and (L)-N-Boc-Leucine) and purification by chromatography on silica gel (hexane:EtOAc, 2:1) to afford **76** (100.1 mg, 91%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.24-7.08 (m, 4H), 6.68-6.64 (m, 2H), 4.92 (m, 2H), 4.57 (m, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 3.40 (s, 3H), 3.39 (s, 3H), 3.02 (br t, 2H), 1.87-1.85 (m, 2H), 1.87-1.85 (m, 3H), 1.70-1.61 (m, 3H), 1.58 (br s, 27 H), 1.05-0.98 (m, 18 H).

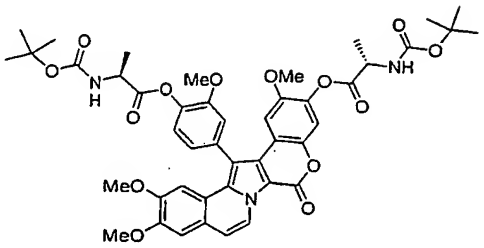
^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4 (2C), 155.5, 155.4, 155.3, 155.0, 152.1, 151.8, 147.5, 144.8, 141.4, 141.0, 139.8, 138.7, 134.8, 134.2, 127.1, 123.8, 123.2, 122.7, 119.5, 116.1, 115.7, 114.7 (2C), 111.8, 107.6, 105.4 (2C), 80.2, 80.0 (2C), 60.7, 56.1, 55.7, 55.5, 52.3 (3C),

41.9, 41.6, 41.5, 41.2, 29.6, 28.3 (9C), 24.7 (3C), 22.9 (2C), 22.8 (2C), 22.7, 21.8.

MS (ESI) m/z: 1193 $(M+23)^+$, 1171 $(M+1)^+$.

Rf: 0.29 (hexane:EtOAc, 2:1).

Compound **77**



General procedure **D** (starting from **26** and (L)-N-Boc-Alanine) and purification by chromatography on silica gel (CH_2Cl_2:MeOH, 60:1) to afford **77** (12.4 mg, 62%).

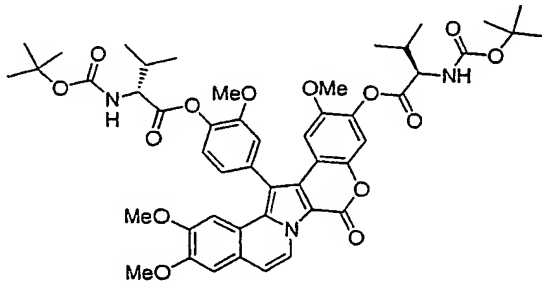
^1H NMR (300 MHz, $CDCl_3$) δ 9.24 (d, J= 7.6 Hz, 1H), 7.34-7.08 (m, 7H), 6.74 (d, J= 8.1 Hz, 1H), 5.30-5.12 (m, 2H), 4.62-4.60 (m, 2H), 4.00 (s, 3H), 3.80 (s, 3H), 3.51 (s, 3H), 3.44 (s, 3H), 1.64-1.44 (m, 24H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 155.0, 152.2, 150.3, 149.6, 147.5, 145.5, 140.0, 139.4, 134.8, 134.2 (2C), 128.3 (2C), 124.7, 123.8, 123.2. 119.0, 116.0, 115.3, 113.0, 112.0, 110.9, 108.4, 107.5, 106.2, 105.1, 80.1, 56.2, 56.0, 55.8, 55.7, 49.3, 28.3, 18.7.

MS (ESI) m/z: 878 $(M+23)^+$, 856 $(M+1)^+$.

Rf: 0.13 (CH_2Cl_2:MeOH, 60:1).

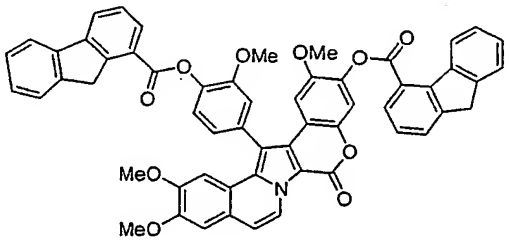
Compound **78**



General procedure **D** (starting from **26** and (D)-N-Boc-Valine) and purification by chromatography on silica gel (CH_2Cl_2:MeOH, 60:1) to afford **78** (15.4 mg, 86%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.23 (d, J= 7.3 Hz, 1H), 7.32-7.22 (m, 3H), 7.14-7.07 (m, 4H), 6.68 (d, J= 8.8 Hz, 1H), 5.09-5.06 (m, 2H), 4.57-4.52 (m, 2H), 3.99 (s, 3H), 3.80 (s, 3H), 3.51 (s, 3H), 3.43 (s, 3H), 2.46-2.38 (m, 2H), 1.49-1.45 (m, 18H), 1.27-1.00 (m, 12H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 155.7, 155.0, 152.2, 150.3, 149.6, 147.5, 145.5, 139.9, 139.3, 134.9, 130.3, 134.8, 134.2, 128.2, 124.7, 123.7, 123.8, 123.1, 119.0, 116.0, 115.3, 113.0, 112.1, 110.9, 108.4, 107.5, 106.2, 105.1, 80.0 (2C), 58.6, 58.5, 56.0, 55.7, 55.6, 55.5, 31.3, 31.2, 28.3 (6C), 19.2, 19.1, 17.2, 17.1.
MS (ESI) m/z: 934 $(M+23)^+$, 912 $(M+1)^+$.
Rf: 0.32 (CH_2Cl_2:MeOH, 60:1).

Compound **79**

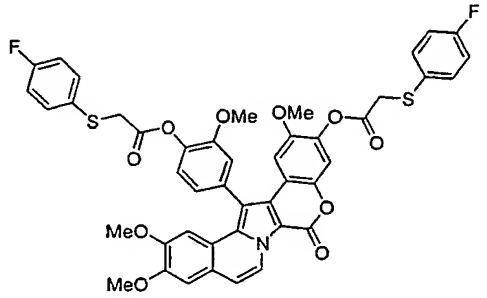


General procedure **D** (starting from **26** and 9H-fluorene-4-carboxilic acid) and purification by chromatography on silica gel (hexane:EtOAc, from 2:1 to 1:1) to afford **79** (8.6 mg, 41%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.31 (d, J= 7.3 Hz, 1H), 8.53-8.45 (m, 2H), 8.21 (d, J= 7.8 Hz, 1H), 8.20 (d, J= 8.0 Hz, 1H), 7.71 (t, J= 7.1 Hz, 2H), 7.61-7.53 (m, 3H), 7.47-7.32 (m, 10H), 7.16-7.13 (m, 2H), 7.05 (s, 1H), 4.02 (s, 3H), 3.99 (s, 2H), 3.96 (s, 2H), 3.90 (s, 3H), 3.66 (s, 3H), 3.61 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 165.9, 155.2, 152.6, 150.4, 149.6, 148.0, 145.7, 145.2, 145.1, 144.3, 144.2, 141.6, 141.4, 140.5, 140.0, 139.9 (2C), 134.8, 134.3, 129.6, 129.4, 129.1 (2C), 128.5, 127.8, 127.7, 126.9, 126.7, 126.1, 126.0, 125.4, 125.1, 125.0, 124.9, 124.8 (2C), 124.6, 124.2, 124.0, 123.2, 119.1, 116.1, 115.4, 113.0, 112.4, 111.2, 108.5, 107.5, 106.4, 105.2, 56.3, 56.0, 55.9, 55.9, 37.0 (2C).
MS (ESI) m/z: 898 $(M+1)^+$.
Rf: 0.50 (hexane:EtOAc, 50:50).

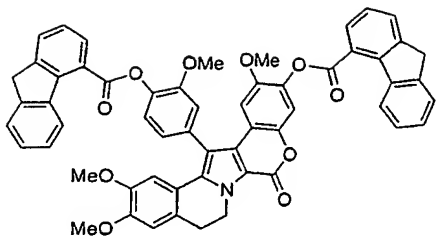
Compound **80**



General procedure **D** (starting from **26** and 2[(4-fluorophenyl)thio]acetic acid) and purification by chromatography on silica gel (hexane:EtOAc, 2:1) to afford **80** (20.4 mg, quant.).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.23 (d, J= 7.3 Hz, 1H), 7.58-7.50 (m, 4H), 7.26-7.20 (m, 4H), 7.11-7.01 (m, 8H), 6.78 (s, 1H), 4.00 (s, 3H), 3.87 (s, 2H), 3.81 (s, 2H), 3.77 (s, 3H), 3.48 (s, 3H), 3.37 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 164.2, 161.0, 154.9, 152.1, 150.3, 149.5, 147.5, 145.4, 139.9, 139.3, 134.9, 134.2, 133.9, 133.8, 133.8, 133.7, 129.3, 128.1, 125.0, 124.7, 123.8, 123.6, 123.1, 118.9, 116.4, 116.1, 115.4, 113.0, 111.9, 110.8, 108.4, 107.5, 106.2, 105.0, 56.2, 56.0, 55.6, 55.5, 37.5, 37.4.
MS (ESI) m/z: 872 $(M+23)^+$, 850 $(M+1)^+$.
Rf: 0.52 (hexane:EtOAc, 2:1).

Compound **81**



General procedure **K** (starting from **95** and 9H-fluorene-4-carboxilic acid) and chromatography on silica gel (CH_2Cl_2:MeOH, 200:1) to afford **81** as a yellow solid (20.0 mg, 95%).

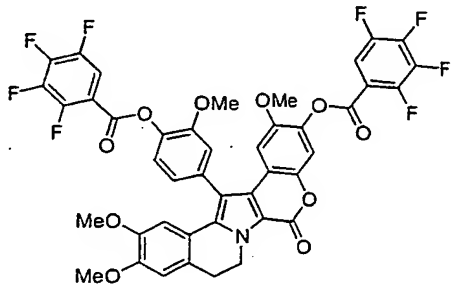
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53-8.43 (m, 2H), 8.17 (m, 2H), 7.78-7.41 (m, 2H), 7.30-7.10 (m, 12H), 6.94 (s, 1H), 6.83 (s, 1H), 6.80 (s, 1H), 4.96-4.80 (m, 2H), 3.98 (s, 2H), 3.96 (s, 2H), 3.93 (s, 3H), 3.88 (s, 3H), 3.60 (s, 3H), 3.54 (s, 3H), 3.19 (t, J= 6.1 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 155.2, 152.5, 149.2, 147.9, 147.8, 145.2, 145.1, 144.3, 144.1, 141.5, 141.3, 140.3, 139.9, 139.1, 136.0, 134.5, 129.5, 129.3, 129.0, 127.7, 127.6, 127.4, 127.3, 127.2, 126.8, 126.7, 126.6, 126.5, 126.1, 126.0, 125.9, 125.4, 125.2, 125.1, 125.0, 124.7, 124.5, 124.0, 123.5, 121.5, 119.7, 116.3, 115.0, 114.5, 112.1, 111.0, 108.6, 105.7, 56.2, 55.9, 55.9, 55.6, 42.6, 37.0 (2 C), 28.6.

MS (ESI) m/z: 922 $(M+23)^+$, 900 $(M+1)^+$.

Rf: 0.44 (CH_2Cl_2:MeOH, 200:1).

Compound **82**



General procedure **K** (starting from **95** and 2,3,4,5-tetrafluorobenzoic acid) and chromatography on silica gel (CH_2Cl_2:MeOH, 200:1) to afford **82** as a yellow solid (20.7 mg, quant.).

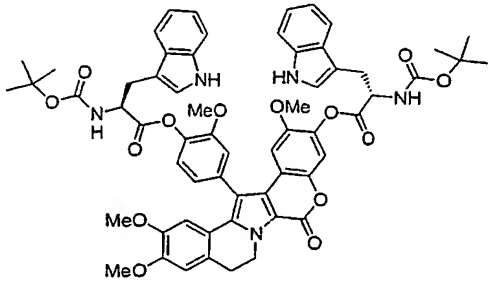
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81-7.76 (m, 2H), 7.35 (d, J_{H-F}= 7.8 Hz, 1H), 7.25-7.20 (m, 3H), 6.79 (br s, 2H), 6.71 (s, 1H), 4.92-4.79 (m, 2H), 3.91 (s, 3H), 3.82 (s, 3H), 3.48 (s, 3H), 3.46 (s, 3H), 3.16 (t, J= 7.3 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7 (2C), 155.0, 152.0, 150.2 (m), 149.3, 148.2 (m), 147.7, 147.4, 146.7 (m), 145.8 (m), 145.0 (m), 144.9, 143.4 (m), 142.3 (m), 140.0 (m), 139.4, 138.2, 136.0, 135.0, 127.0, 126.6, 123.6, 123.5, 119.5, 116.7, 115.1, 114.7, 114.6, 113.6 (m), 111.8, 111.0, 108.5, 105.6, 56.3, 55.9, 55.8, 55.5, 42.5, 28.6.

MS (ESI) m/z: 889 $(M+23)^+$, 867 $(M+1)^+$.

Rf: 0.25 (CH_2Cl_2:MeOH, 200:1).

Compound **83**



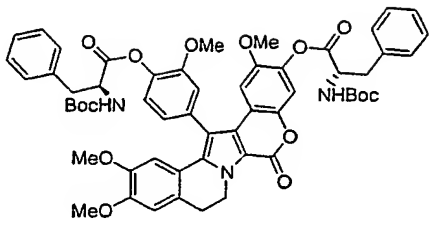
General procedure **K** (starting from **95** and (L)-N-Boc-Tryptophane) and chromatography on silica gel (CH_2Cl_2:MeOH, 25:1) to afford **83** as a yellow solid (13.0 mg, 98%).

^{1}H NMR (300 MHz, $CDCl_3$) δ8.25-8.23 (br d, 2H), 7.68-7.63 (m, 2H), 7.40-7.34 (m, 2H), 7.26-7.05 (m, 7H), 6.93 (s, 1H), 6.77 (s, 1H), 6.67 (br s, 2H), 4.95-4.74 (m, 4H), 3.90 (s, 3H), 3.75 (s, 3H), 3.57-3.50 (m, 4H), 3.82 (s, 3H), 3.36 (s, 3H), 3.13 (br t, J= 6.6 Hz, 2H), 1.43 (br d, 18H).

MS (ESI) m/z: 1110 $(M+23)^+$.

Rf: 0.11 (CH_2Cl_2:MeOH, 30:1).

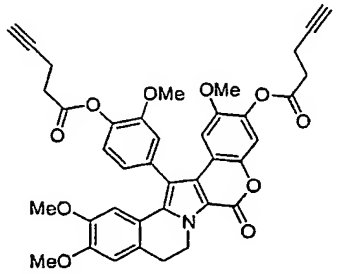
Compound **84**



General procedure **K** (starting from **95** and (L)-N-Boc-Phenylalanine) and chromatography on silica gel (CH_2Cl_2:MeOH, 60:1) to afford **84** as a yellow solid (13.0 mg, 96%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.20 (m, 9H), 7.17-7.04 (m, 5H), 6.77 (s, 1H), 6.79-6.66 (m, 2H), 5.02-4.74 (m, 4H), 3.90 (s, 3H), 3.80 (s, 3H), 3.40 (s, 3H), 3.39 (s, 3H), 3.34-3.12 (m, 6H), 1.44-138 (m, 18H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 154.9, 151.9, 149.1, 147.6, 147.4, 144.7, 139.4, 138.3, 135.8, 134.4, 129.4, 129.2, 128.5, 127.1, 126.4, 126.3, 123.6, 123.3, 119.5, 116.3, 114.9, 114.6, 114.4, 111.7, 110.9, 108.4, 105.4, 79.9 (2C), 56.0, 55.8, 55.6, 55.4, 54.3 (2C), 42.4, 38.0 (2C), 28.4, 28.2 (6C).
MS (ESI) m/z: 1032 $(M+23)^+$.
Rf: 0.76 (CH_2Cl_2:MeOH, 60:1).

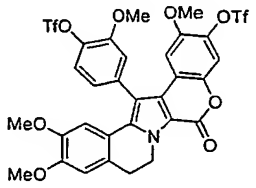
Compound **85**



General procedure **K** (starting from **95** and 4-pentynoic acid) and chromatography on silica gel (CH_2Cl_2:MeOH, 60:1) to afford **85** as a yellow solid (9.0 mg, 99%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.21 (m, 2H), 7.15-7.10 (m, 2H), 6.76 (s, 1H), 6.71 (s, 1H), 6.68 (s, 1H), 4.89-4.30 (m, 2H), 3.89 (s, 3H), 3.42 (s, 3H), 3.42 (s, 3H), 3.40 (s, 3H), 3.23 (t, J= 7.1 Hz, 2H), 2.89-2.80 (m, 4H), 2.69-2.59 (m, 4H), 2.05-2.03 (m, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 169.5, 155.1, 152.1, 149.1, 147.7, 147.6, 144.9, 139.8, 138.7, 135.9, 134.4, 130.9, 128.8, 127.2, 126.4, 123.8, 123.3, 119.6, 116.2, 114.8, 114.5, 111.9, 111.0, 108.5, 105.5, 82.1, 82.0, 69.3 (2C), 56.2, 55.9, 55.7, 55.4, 42.5, 33.1 (2C), 28.6.
MS (ESI) m/z: 698 $(M+23)^+$, 676 $(M+1)^+$.
Rf: 0.65 (CH_2Cl_2:MeOH, 60:1).

Compound **86**



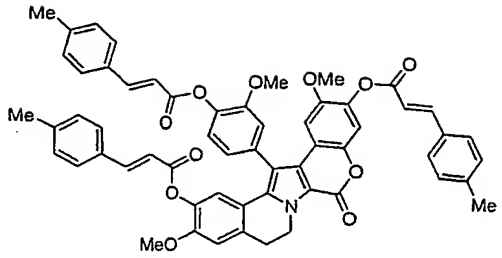
General procedure **I** (starting from **95**) and chromatography on silica gel (CH_2Cl_2) to give **86** as a yellow solid (13.4 mg, 89%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J= 8.8 Hz, 1H), 7.27 (s, 1H), 7.24-7.20 (m, 2H), 6.79 (s, 1H), 6.66 (s, 1H), 6.54 (s, 1H), 4.93-4.86 (m, 1H), 4.77-4.70 (m, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.47 (s, 3H), 3.36 (s, 3H), 3.15 (br t, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 152.5, 149.6, 147.8 (2C), 144.4, 138.5, 137.0 (3C), 136.2, 129.7, 126.8, 126.1, 123.6, 123.5, 118.6 (q, J_{C-F}= 136.7 Hz), 118.6 (q, J_{C-F}= 132.2 Hz), 115.7, 114.9, 114.0, 111.9, 111.2, 108.3, 105.7, 56.6, 56.0, 55.8, 55.2, 42.6, 28.5.

MS (ESI) m/z: 780 $(M+1)^+$.

Rf: 0.43 (CH_2Cl_2).

Compound **87**



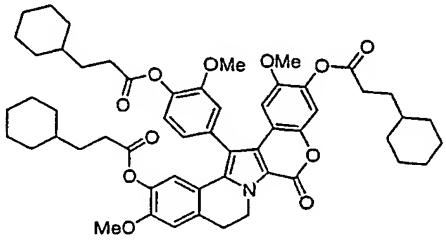
General procedure **K** (starting from **167** and 4-methylcinnamic acid) and chromatography on silica gel (hexane:EtOAc, 1:1) to afford **87** as a white solid (5.5 mg, 86%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J=16.4 Hz, 1H), 7.79 (d, J= 16.8 Hz, 1H), 7.75 (d, J= 15.8 Hz, 1H), 7.52-7.47 (m, 4H), 7.43-7.40 (m, 2H), 7.28-7.10 (m, 10H), 6.91 (s, 1H), 6.87 (s, 1H), 6.77 (s, 1H), 6.60 (d, J= 16.1 Hz, 1H), 6.58 (d, J= 16.1 Hz, 1H), 6.57 (d, J= 16.1 Hz, 1H), 4.96-4.90 (m, 1H), 4.82-4.78 (m, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.50 (s, 3H), 3.21 (t, J= 7.1 Hz, 2H), 2.39 (s, 9H).

MS (ESI) m/z: 956 $(M+23)^+$, 934 $(M+1)^+$.

Rf: 0.45 (hexane:EtOAc, 1:1).

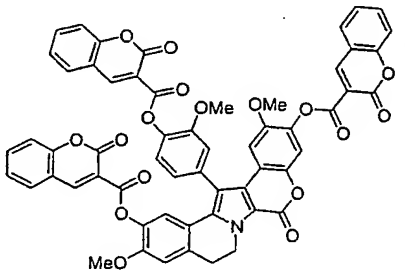
Compound **88**



General procedure **K** (starting from **167** and cyclohexilpropionic acid) and chromatography on silica gel (hexane:EtOAc, 1:1) to afford **88** as a yellow oil (4.5 mg, quant.).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.15 (m, 1H), 7.08-7.03 (m, 3H), 6.86 (s, 1H), 6.72-6.69 (m, 2H), 4.93-4.87 (m, 1H), 4.76-4.71 (m, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.43 (s, 3H), 3.17 (br t, 2H), 2.64-2.55 (m, 6H), 1.77-1.40 (m, 21H), 1.36-1.02 (m, 12H), 0.98-0.88 (m, 6H).
MS (ESI) m/z: 938 $(M+23)^+$, 916 $(M+1)^+$.
Rf: 0.63 (hexane:EtOAc, 1:1).

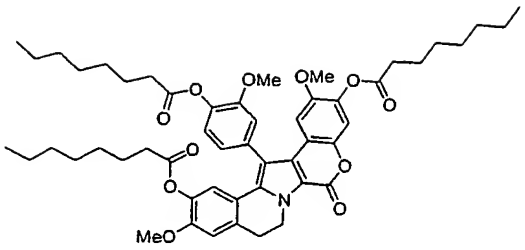
Compound **89**



General procedure **K** (starting from **167** and coumarin-3-carboxylic acid), chromatography on silica gel (CH_2Cl_2:MeOH, 20:1) and the yellow solid was triturated with MeOH to afford **89** as a bright yellow solid (9.2 mg, 86%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.75 (s, 1H), 8.70 (s, 1H), 7.77-7.62 (m, 6H), 7.37-7.33 (m, 6H), 7.24-7.13 (m, 4H), 6.93 (s, 1H), 6.87 (s, 1H), 6.80 (s, 1H), 4.92 (m, 1H), 4.84 (m, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.50 (s, 3H), 3.23 (br t, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 160.4 (2C), 156.5 (2C), 155.5, 155.4, 155.1, 152.1, 151.2, 150.3 (2C), 147.7, 144.9, 139.7, 138.6, 138.2, 134.9 (4C), 134.7, 133.9, 133.3, 130.2, 129.8 (2C), 127.1, 125.0, 124.9, 124.1, 123.2, 120.3, 120.1, 117.9, 117.8, 117.1, 116.9 (2C), 116.7, 116.5, 115.5, 114.8, 112.3, 112.1, 105.6, 56.3, 56.2 (2C), 42.2, 29.3.
MS (ESI) m/z: 1017 $(M)^+$.
Rf: 0.24 (CH_2Cl_2:MeOH, 40:1).

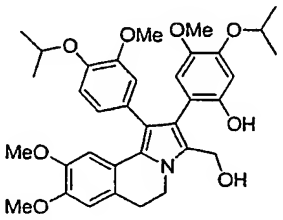
Compound **90**



General procedure **K** (starting from **167** and *n*-octanoic acid) and chromatography on silica gel (hexane:EtOAc, 2:1) to afford **90** as a yellow oil (7.8 mg, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-7.15 (m, 1H), 7.08-7.02 (m, 3H), 6.86 (s, 1H), 6.72-6.69 (m, 2H), 4.93-4.89 (m, 1H), 4.76-4.72 (m, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.43 (s, 3H), 3.17 (br t, 2H), 2.63-2.47 (m, 6H), 1.78-1.69 (m, 6H), 1.32-1.25 (m, 18H), 0.90-0.88 (m, 15H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 171.7, 171.4, 155.2, 152.2, 151.2, 147.8, 144.9, 142.6, 140.0, 139.0, 138.5, 133.3, 132.7, 127.3, 123.9, 123.1, 123.0, 120.3, 116.0, 115.4, 114.6, 113.3, 112.1, 111.9, 105.5, 56.1, 55.9, 55.8, 42.2, 34.0, 33.9, 33.8, 31.7 (2C), 31.6, 29.2, 29.0, 28.9 (5C), 25.1, 24.9 (2C), 22.6 (3C), 14.1 (3C).
MS (ESI) m/z: 902 $(M+23)^+$, 880 $(M+1)^+$.
Rf: 0.38 (hexane: EtOAc, 2:1).

Compound **91**

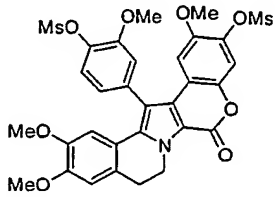


A solution of **162** (6.0 mg, 0.01 mmol) was added to a suspension of $NaBH_4$ (1.0 mg, 0.02 mmol) in anhydrous THF (2 mL) at 0 °C under Argon atmosphere. The reaction mixture was stirred at 23 °C for 3 h, then H_2O (5 mL) was slowly added at 0 °C. The mixture was extracted with CH_2Cl_2 (3x10 mL), dried over anhydrous Na_2SO_4, filtered, and

evaporated under reduced pressure to give **91** as a white solid (6.0 mg, quant).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.80 (br s, 2H), 6.80 (s, 1H), 6.72 (s, 1H), 6.67 (s, 1H), 6.51 (s, 1H), 6.42 (s, 1H), 4.59 (s, 2H), 4.49-4.44 (m, 2H), 4.28-4.00 (m, 2H), 3.88 (s, 3H), 3.58 (s, 3H), 3.54 (s, 3H), 3.40 (s, 3H), 3.07 (m, 2H), 1.36 (d, J= 6.1 Hz, 6H), 1.31 (d, J= 6.1 Hz, 6H).
MS (ESI) m/z: 626 $(M+23)^+$.
Rf: 0.10 (CH_2Cl_2:MeOH, 20:1).

Compound **92**



A suspension of **95** (7.0 mg, 0.0135 mmol), methanesulfonyl chloride (6 mL, 0.077 mmol), pyridine (6 mL, 0.077 mmol) and DMAP (1 mg, 0.008 mmol) in anhydrous CH_2Cl_2 (2 mL) was stirred at 23 °C for 48 h under Argon atmosphere. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel (CH_2Cl_2:MeOH, 20:1) to give **92** as a yellow solid (7.5 mg, 83%).

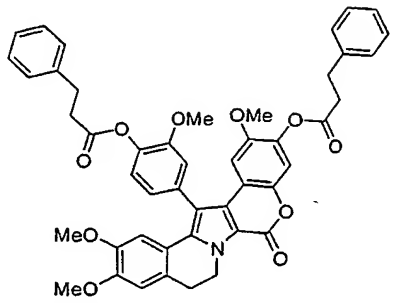
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J= 8.1 Hz, 1H), 7.32 (br s, 1H), 7.21 (br d, J= 8.1 Hz, 1H), 7.14 (br s, 1H), 6.77 (s, 1H), 6.68 (s, 1H), 6.61 (s, 1H), 4.99-4.94 (m, 1H), 4.70-4.66 (m, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.46 (s, 3H), 3.37 (s, 3H), 3.31 (s, 3H), 3.19 (s, 3H), 3.12 (br t, J= 6.3 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 152.6, 149.4, 148.0, 147.7, 144.8, 138.0, 137.0, 135.9 (2C), 126.7, 125.5, 123.7, 119.3, 117.3, 115.5,

113.7, 111.1, 108.4, 105.7, 56.4, 56.0, 55.8, 55.3, 42.5, 39.1, 38.6, 29.7.

MS (ESI) m/z: 694 $(M+23)^+$, 672 $(M+1)^+$.

Rf: 0.50 (CH_2Cl_2:MeOH, 20:1).

Compound **93**



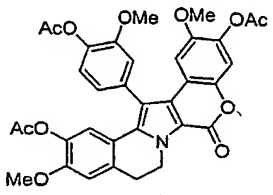
General procedure **F** (starting from **95** and hydrocinnamoyl chloride) and chromatography on silica gel (hexane:EtOAc, 1:1) to afford **93** as a white solid (4.9 mg, 43%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.22 (m, 9 H), 7.15-7.02 (m, 3H), 6.76 (s, 1H), 6.70 (s, 1H), 6.68 (s, 1H), 4.90-4.74 (m, 2H), 3.90 (s, 3H), 3.75 (s, 3H), 3.40 (s, 3H), 3.38 (s, 3H), 3.16-2.89 (m, 10H).

MS (ESI) m/z: 802 $(M+23)^+$, 780 $(M+1)^+$.

Rf: 0.38 (hexane:EtOAc, 1:1).

Compound **94**



General procedure **L** (starting from **167** and Ac_2O) to afford **94** as a brown solid (11.0 mg, 91%.).

^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, J= 7.8 Hz, 1H), 7.09-7.04 (m, 3H), 6.87 (s, 1H), 6.70 (br s, 2H), 4.92-4.86 (m, 1H), 4.79-4.72 (m, 1H), 3.85

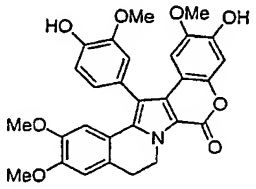
(s, 3H), 3.79 (s, 3H), 3.43 (s, 3H), 3.17 (t, *J*= 6.3 Hz, 2H), 2.35 (s, 3H), 2.23 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 168.8, 168.5, 155.1, 152.1, 151.1, 147.7, 144.8, 139.9, 138.8, 138.4, 134.9, 133.4, 132.9, 127.2, 123.9, 123.1, 120.3, 120.0, 116.1, 115.4, 114.6, 112.1, 111.9, 105.5, 56.1, 56.0, 55.8, 42.1, 29.2, 20.6 (2C), 20.5.

MS (ESI) m/z: 650 $(M+23)^+$, 628 $(M+1)^+$.

Rf: 0.28 (hexane:EtOAc, 1:1).

Compound **95**



General procedure **A** (starting from **162**) and chromatography on silica gel (CH_2Cl_2:MeOH, 20:1) to afford **95** as a yellow solid (170 mg, 61%).

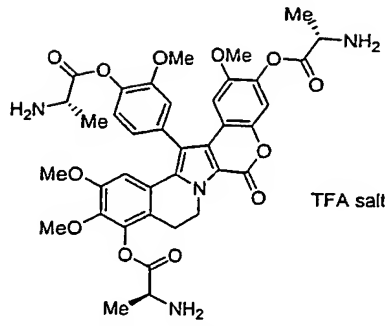
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14-7.07 (m, 2H), 6.07-6.96 (m, 2H), 6.76 (s, 1H), 6.71 (s, 1H), 6.64 (s, 1H), 5.75 (s, 1H), 5.72 (s, 1H), 4.98-4.89 (m, 1H), 4.69-4.59 (m, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.50 (s, 3H), 3.38 (s, 3H), 3.15-3.09 (m, 2H).

^{13}C NMR (75 MHz, DMSO-d_6) δ 154.3, 148.8, 148.5, 147.0, 146.9, 146.6, 145.7, 144.5, 135.5, 127.7, 126.8, 125.4, 123.4, 119.4, 116.3, 114.7, 112.5, 111.7, 108.7, 105.0, 103.6, 56.0, 55.5, 55.1, 54.5, 42.0, 27.7.

MS (ESI) m/z: 516 $(M+1)^+$.

Rf: 0.33 (CH_2Cl_2:MeOH, 20:1).

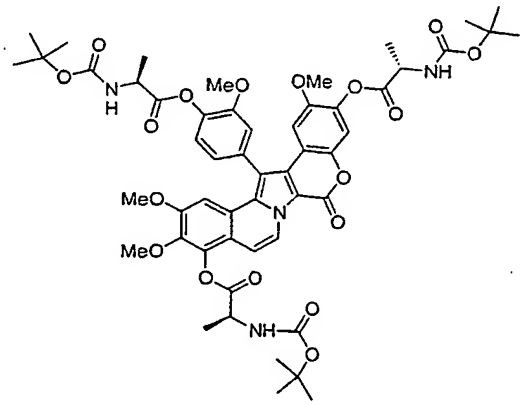
Compound **96**



General procedure **B** (starting from **46**) to afford **96.**

^{1}H NMR (300 MHz, CD_3OD) δ 7.60-7.40 (m, 2H), 7.40-7.20 (m, 2H), 7.00-6.80 (m, 2H), 4.77 (br s, 2H), 4.75-4.40 (m, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 3.44 (s, 3H), 3.42 (s, 3H), 3.05 (br s, 2H), 2.00-1.70 (m, 9H).
MS (ESI) m/z: 745 $(M+1)^+$.

Compound **97**

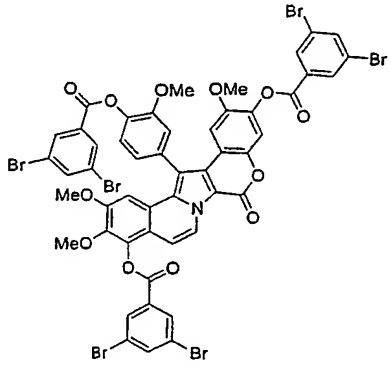


General procedure **E** (starting from **46**, reaction time 30 h) and chromatography on silica gel (hexane:EtOAc, 1:1) to afford **97** as a yellow solid (16 mg, 88%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.23 (d, J= 7.6 Hz, 1H), 7.40-7.05 (m, 6H), 6.78 (d, J= 8.4 Hz, 1H), 5.20-5.00 (m, 3H), 4.80-4.50 (m, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.48 (s, 3H), 3.43 (s, 3H), 1.68 (d, J= 7.1 Hz, 3H), 1.62 (d, J= 7.2 Hz, 3H), 1.55 (d, J=7.1 Hz, 3H), 1.49 (s, 18H), 1.46 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 171.6, 171.3, 155.3, 155.0, 154.9, 153.1, 152.2, 147.6, 145.5, 145.4, 141.6, 140.0, 139.5, 138.8, 134.5, 133.2, 128.3, 128.2, 123.9, 123.6, 123.5, 121.0, 118.3, 115.8, 115.1, 112.1, 109.0, 106.8, 106.2, 104.2, 80.3, 80.1 (2C), 60.8, 56.2, 55.8, 55.6, 49.6, 49.3 (2C), 28.3 (9C), 18.6 (2C), 18.3.
MS (ESI) m/z: 1043 $(M)^+$.
Rf: 0.42 (hexane:EtOAc, 1:1).

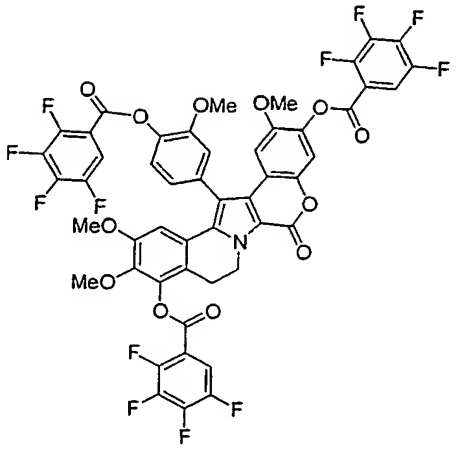
Compound **98**



General procedure **E** (starting from **141**, reaction time 18 h) and chromatography on silica gel (CH_2Cl_2) to afford **98** as a white solid (4 mg, 66%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.25 (d, J= 7.6 Hz, 1H), 8.39 (d, J= 1.8 Hz, 2H), 8.32 (d, J= 1.8 Hz, 2H), 8.27 (d, J= 1.8 Hz, 2H), 8.01 (t, J= 1.8 Hz, 1H), 7.97 (t, J= 1.8 Hz, 1H), 7.94 (t, J= 1.8 Hz, 1H), 7.43 (d, J= 8.0 Hz, 1H), 7.40-7.25 (m, 3H), 7.19 (s, 1H), 7.09 (d, J= 7.6 Hz, 1H), 6.91 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.60 (s, 3H), 3.52 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 162.1, 162.0, 154.9, 153.3, 152.4, 147.7, 145.5, 141.9, 140.1, 139.5, 139.4, 139.0, 138.8, 134.8, 133.2, 132.2, 132.1, 132.0, 131.9, 131.8, 130.9, 128.8, 128.3, 124.0, 123.7, 123.6, 123.5, 123.3, 123.2, 121.0, 118.1, 116.1, 115.2, 112.2, 109.1, 106.5, 106.3, 104.5, 61.0, 56.3, 55.9, 55.8. MS (APCI) m/z: 1315 $(M)^+$.
Rf: 0.73 (CH_2Cl_2).

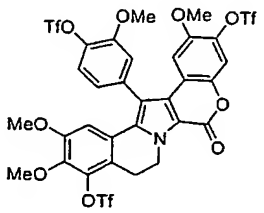
Compound **99**



General procedure **D** (starting from **1**, 2,3,4,5-tetrafluorobenzoic acid) and chromatography on silica gel (CH_2Cl_2:MeOH, 200:1) to afford **99** as a white solid (35 mg, 71%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90-7.70 (m, 3H), 7.38 (d, J= 8.0 Hz, 1H), 7.30-7.15 (m, 3H), 6.76 (s, 2H), 5.00-4.80 (br s, 1H), 4.80-4.60 (br s, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.48 (s, 3H), 3.47 (s, 3H), 3.05 (br s, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 155.2, 152.3, 152.2, 147.7, 145.2, 141.4, 141.3, 139.7, 138.6, 135.0, 127.2, 124.0, 123.6, 123.0, 119.2, 116.7, 116.0, 115.3, 115.1, 114.2, 113.9, 112.1, 108.3, 105.8, 61.2, 56.6, 56.1, 55.9, 42.1, 22.6.
MS (ESI) m/z: 1059 $(M)^+$.
Rf: 0.46 (CH_2Cl_2).

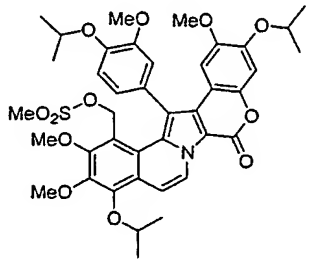
Compound **100**



General procedure **I** (starting from **1**) and chromatography on silica gel (CH_2Cl_2) to afford **100** as a white solid (30 mg, 85%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J= 8.6 Hz, 1H), 7.30-7.20 (m, 3H), 6.63 (s, 1H), 6.62 (s, 1H), 5.00-4.90 (m, 1H), 4.80-4.60 (m, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.47 (s, 3H), 3.37 (s, 3H), 3.25-3.15 (m, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 152.7, 152.0, 147.9, 144.4, 141.7, 140.3, 138.7, 137.2, 136.5, 134.1, 126.1, 123.7, 123.4, 122.4, 120.7, 119.3, 117.8, 116.4, 115.4, 112.1, 109.0, 105.7, 61.4, 56.7, 55.8, 55.5, 41.8, 22.6.
MS (ESI) m/z: 927 $(M)^+$.
Rf: 0.57 (CH_2Cl_2).

Compound **101**

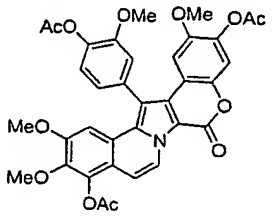


General procedure **G** (starting from methanesulfonic acid 5-isopropoxy-6,7-dimethoxy-isoquinolin-8-ylmethyl ester) and chromatography on silica gel (hexane:EtOAc, from 3:1 to 1:1) to afford **101** as a white solid (4 mg, 19%).

^1H NMR (300 MHz, $CDCl_3$) δ 9.22 (d, J= 7.5 Hz, 1H), 7.38 (d, J= 7.5 Hz, 1H), 7.26 (s, 1H), 7.05 (s, 2H), 7.00-6.90 (m, 2H), 4.80-4.50 (m, 3H), 3.95 (s, 5H), 3.85 (s, 3H), 3.75 (s, 3H), 3.54 (s, 2H), 2.92 (s, 3H), 1.50-1.30 (m, 18H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 154.3, 151.0, 147.8, 146.8, 146.6, 146.4, 146.2, 140.7, 140.2, 134.7, 128.9, 128.8, 124.3, 124.0, 123.7,

123.1, 120.2, 116.5, 116.2, 115.4, 109.8, 107.7, 105.7, 103.4, 77.2, 71.7, 71.4, 68.6, 61.6, 60.6, 57.6, 56.0, 55.8, 22.8, 22.0, 21.8.
MS (ESI) m/z: 722 $(M-^{i}Pr)^{+}$.
Rf: 0.50 (hexane:EtOAc, 1:1).

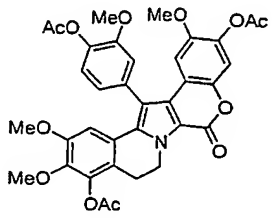
Compound **102**



General procedure **L** (starting from **2** and Ac_2O) and chromatography on silica gel (hexane:EtOAc, 1:1) to afford **102** as a white solid (5.4 mg, 96%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (d, J= 7.6 Hz, 1H), 7.40-7.00 (m, 6H), 6.81 (s, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.48 (s, 3H), 3.45 (s, 3H), 2.49 (s, 3H), 2.37 (s, 3H), 2.32 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 168.7, 155.0, 153.2, 152.4, 147.8, 145.5, 141.9, 140.3, 139.8, 139.0, 134.3, 133.3, 128.4, 124.1, 123.6, 123.4, 121.0, 118.2, 115.7, 115.1, 112.2, 112.1, 109.0, 106.6, 106.1, 104.1, 60.8, 56.2, 55.7, 55.6, 20.6 (3C).
MS (ESI) m/z: 678 $(M+23)^{+}$.
Rf: 0.38 (hexane:EtOAc, 1:1).

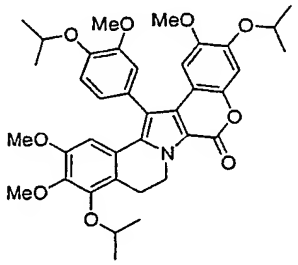
Compound **103**



General procedure **L** (starting from **1** and Ac_2O) and chromatography on silica gel (hexane:EtOAc, 1:2) to afford **103** as a white solid (12 mg, 99%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.05 (m, 4H), 6.68 (s, 2H), 4.95-4.80 (m, 1H), 4.80-4.60 (m, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.42 (s, 3H), 3.38 (s, 3H), 3.00-2.95 (m, 2H), 2.40 (s, 3H), 2.35 (s, 3H), 2.31 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 168.8, 168.7, 155.1, 152.2, 151.8, 147.7, 144.9, 141.6, 141.2, 140.0, 138.9, 134.9, 134.1, 127.2, 123.9, 123.2, 122.6, 119.1, 116.0, 115.8, 114.8, 114.7, 111.9, 107.5, 105.4, 60.8, 56.2, 55.7, 55.4, 41.9, 22.2, 20.6 (2C), 20.5.
MS (ESI) m/z: 680 $(M+23)^+$.
Rf: 0.32 (hexane:EtOAc, 1:1).

Compound **104**



General procedure **H** (starting from 6,7-dimethoxy-5-isopropoxy-3,4-dihydroisoquinoline) and chromatography on silica gel (hexane:CH_2Cl_2:Et_2O, from 5:5:1 to 5:5:2) to afford **104** as a white solid (1.58 g, 56%).

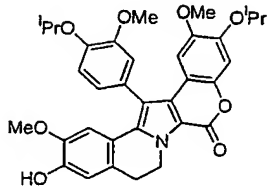
^1H NMR (300 MHz, $CDCl_3$) δ 7.15-7.00 (m, 3H), 6.91 (s, 1H), 6.63 (s, 1H), 6.59 (s, 1H), 4.73 (t, J= 7.0 Hz, 2H), 4.65-4.50 (m, 3H), 3.82 (s, 6H), 3.41 (s, 3H), 3.33 (s, 3H), 3.14 (t, J= 6.8 Hz, 2H), 1.39 (t, J= 6.3 Hz, 12H), 1.31 (d, J= 6.1 Hz, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 151.7, 151.3, 148.6, 147.0, 146.9, 146.5, 145.9, 142.5, 135.5, 128.6, 128.1, 123.4, 123.0, 121.1, 116.9,

115.6, 114.6, 113.8, 110.3, 104.9, 104.8, 103.5, 75.7, 71.8, 71.4, 60.5, 56.2, 55.4, 55.1, 42.3, 22.7, 21.9, 21.8.

MS (ESI) m/z: 658 $(M+1)^+$.

Rf: 0.56 (hexane:EtOAc, 1:1).

Compound **105**



General procedure **J** (starting from **163**, reaction time 22 h) and chromatography on silica gel (hexane:EtOAc, 1:1) to afford **105** (10 mg, 56%).

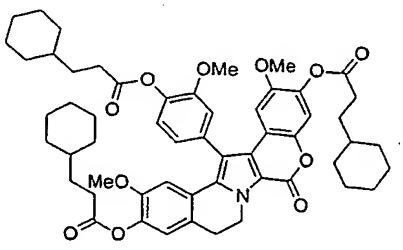
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12-7.03 (m, 3H), 6.92 (s, 1H), 6.81 (s, 1H), 6.69 (s, 1H), 6.67 (s, 1H), 4.85-4.69 (m, 2H), 4.64-4.40 (m, 2H), 3.82 (s, 3H), 3.43 (s, 3H), 3.39 (s, 3H), 3.08 (t, J= 6.6 Hz, 2H), 1.42-1.37 (m, 12H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 151.3, 147.0, 146.9, 146.5, 146.0, 145.8, 145.1, 136.0, 129.3, 128.7, 128.2, 127.5, 125.0, 123.4, 119.7, 116.9, 114.6, 114.2, 110.4, 108.3, 104.9, 103.5, 71.8, 71.4, 56.2, 55.5, 55.3, 42.4, 28.5, 21.9 (2C), 21.8 (2C).

MS (ESI) m/z: 608 $(M+23)^+$, 586 $(M+1)^+$.

Rf: 0.30 (hexane:EtOAc, 1:1).

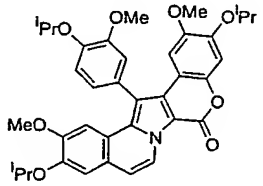
Compound **106**



General procedure **D** (starting from **109** and cyclohexanepropionic acid) and chromatography on silica gel (CH_2Cl_2:MeOH, from 100:1 to 50:1) to afford **106** as a white solid (33 mg, 72%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, J= 7.9 Hz, 1H), 7.14-7.07 (m, 3H), 6.94 (s, 1H), 6.79 (s, 1H), 6.70 (s, 1H), 4.92-4.84 (m, 1H), 4.79-4.70 (m, 1H), 3.80 (s, 3H), 3.42 (s, 3H), 3.35 (s, 3H), 3.11 (t, J= 6.7 Hz, 2H), 2.64-2.54 (m, 6H), 1.81-1.60 (m, 21H), 1.39-1.12 (m, 12H), 0.98-0.91 (m, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 171.9, 171.8, 155.1, 152.3, 149.9, 147.7, 144.9, 140.1, 139.5, 139.0, 135.1, 133.8, 127.1, 125.9, 125.5, 123.9, 123.1, 122.6, 115.9 (2C), 114.8, 114.6, 111.9, 109.7, 105.4, 56.2, 55.7, 55.5, 42.4, 37.2 (3C), 37.1 (3C), 32.9 (6C), 32.2 (3C), 31.6 (3C), 28.0, 26.5 (3C), 26.2 (3C).
MS (APCI) m/z: 916 $(M+1)^+$.
Rf: 0.17 (hexane:EtOAc, 4:1).

Compound **107**



General procedure **E** (starting from **110**, reaction time 2 h) and chromatography on silica gel (hexane:EtOAc, 2:1) to afford **107** (283 mg, 94%).

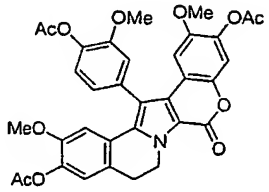
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (d, J= 7.3 Hz, 1H), 7.29-7.17 (m, 2H), 7.12-7.10 (m, 2H), 7.04-7.02 (m, 2H), 6.98 (s, 1H), 6.76 (s, 1H), 4.70-4.56 (m, 3H), 3.84 (s, 3H), 3.44 (s, 3H), 3.43 (s, 3H), 1.44-1.39 (m, 18H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 151.2, 150.0, 148.3, 147.7, 147.0, 146.4, 146.3, 134.2, 129.2, 128.6, 124.6, 123.8, 122.9, 118.8, 116.7,

114.9, 112.1, 110.8, 110.2, 109.8, 107.6, 105.5, 105.3, 103.2, 71.6, 71.3, 71.0, 56.0, 55.3, 55.0, 21.8 (3C), 21.7, 21.7, 21.6.

MS (ESI) m/z: 648 $(M+23)^+$, 626 $(M+1)^+$.

Rf: 0.35 (hexane:EtOAc, 2:1).

Compound **108**



General procedure **L** (starting from **109** and Ac_2O) and chromatography on silica gel (CH_2Cl_2:MeOH, from 50:1 to 40:1) to afford **108** as a white solid (38 mg, 76%).

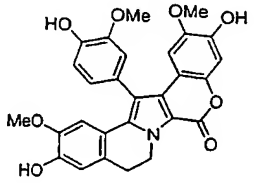
^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J= 7.9 Hz, 1H), 7.15-7.09 (m, 3H), 6.95 (s, 1H), 6.79 (s, 1H), 6.69 (s, 1H), 4.92-4.71 (m, 2H), 3.81 (s, 3H), 3.43 (s, 3H), 3.35 (s, 3H), 3.12 (t, J= 6.7 Hz, 2H), 2.35 (s, 3H), 2.31 (s, 3H), 2.30 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 168.8, 168.6, 155.1, 152.2, 149.9, 147.7, 144.9, 140.0, 139.4, 138.9, 135.0, 134.0, 127.1, 125.9, 125.7, 123.9, 123.2, 122.6, 116.0, 115.9, 114.9, 114.6, 112.0, 109.7, 105.4, 56.2, 55.7, 55.5, 42.5, 28.1, 20.6 (3C).

MS (ESI) m/z: 628 $(M+1)^+$.

Rf: 0.32 (CH_2Cl_2:MeOH, 100:1).

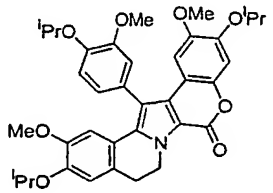
Compound **109**



General procedure **A** (starting from **110**) and chromatography on silica gel (CH_2Cl_2:MeOH, from 20:1 to 10:1 to 5:1) to afford **109** as a pale brown solid (1.11 g, 97%).

^1H NMR (300 MHz, DMSO-d_6) δ 9.64 (s, 1H), 9.41 (s, 1H), 9.24 (s, 1H), 7.01 (s, 1H), 6.99 (d, J= 8.1 Hz, 1H), 6.88 (d, J= 8.4 Hz, 1H), 6.78 (s, 1H), 6.73 (s, 1H), 6.67 (s, 1H), 6.59 (s, 1H), 4.58 (t, J= 6.5 Hz, 2H), 3.73 (s, 3H), 3.34 (s, 3H), 3.25 (s, 3H), 2.99 (t, J= 6.4 Hz, 2H).
^{13}C NMR (75 MHz, DMSO-d_6) δ 154.3, 148.5, 147.1, 146.9, 146.5, 146.0, 145.7, 144.4, 135.9, 127.7, 127.1, 125.5, 123.4, 118.1, 116.3, 115.3, 114.7, 114.3, 112.2, 109.2, 108.8, 105.1, 103.6, 56.0, 55.0, 54.7, 42.0, 27.5.
MS (ESI) m/z: 524 $(M+23)^+$.
Rf: 0.55 (CH_2Cl_2:MeOH 10:1).

Compound **110**

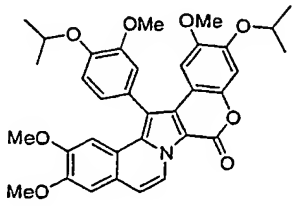


General procedure **H** (starting from 6-Isopropoxy-7-methoxy-3,4-dihydroisoquinoline) and chromatography on silica gel (hexane:CH_2Cl_2:Et_2O, 5:5:2) to afford **110** as a pale yellow solid (1.27 g, 47%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.08-7.04 (m, 3H), 6.92 (s, 1H), 6.76-6.74 (m, 2H), 6.67 (s, 1H), 4.87-4.71 (m, 2H), 4.65-4.48 (m, 3H), 3.82 (s, 3H), 3.42 (s, 3H), 3.33 (s, 3H), 3.09 (t, J= 6.6 Hz, 2H), 1.41-1.36 (m, 18H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 151.2, 148.5, 147.2, 146.9, 146.8, 146.4, 145.8, 135.9, 128.5, 128.1, 126.3, 123.3, 120.1, 116.8, 114.8,

114.6, 114.5, 113.6, 110.3, 109.1, 104.8, 103.4, 71.7, 71.3, 71.2, 56.1, 55.4, 55.0, 42.3, 28.5, 22.0 (2C), 21.8, 21.8, 21.7 (2C).
MS (ESI) m/z: 628 $(M+1)^+$.
Rf: 0.28 (hexane:CH_2Cl_2:Et_2O, 5:5:2).

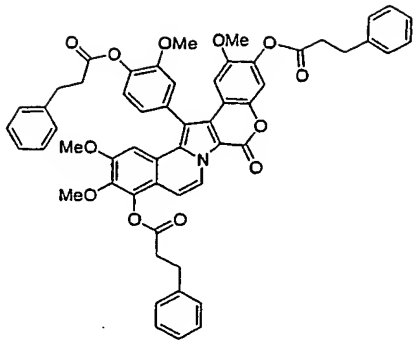
Compound **111**



General procedure **E** (starting from **162**, reaction time 3 h) and chromatography on silica gel (hexane:EtOAc, 1:1) to afford **111** as a white solid (176.3 mg, 94%).

^1H NMR (300 MHz, $CDCl_3$) δ 9.25 (d, J= 7.3 Hz, 1H), 7.19-7.04 (m, 6H), 6.97 (s, 1H), 6.76 (s, 1H), 4.66-4.56 (m, 2H), 3.99 (s, 3H), 3.84 (s, 3H), 3.47 (s, 3H), 3.45 (s, 3H), 1.44-1.40 (m, 12H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 151.3, 150.0, 149.1, 147.8, 147.1, 146.6, 146.5, 134.3, 129.4, 128.6, 124.7, 123.9, 123.3, 119.1, 116.8, 115.0, 112.2, 111.0, 109.9, 107.8, 107.3, 105.4, 105.3, 103.4, 71.7, 71.4, 56.1, 55.9, 55.9, 55.4, 55.1, 21.9, 21.8.
MS (ESI) m/z: 598 $(M+1)^+$.
Rf: 0.50 (hexane:EtOAc, 1:1).

Compound **112**



General procedure **E** (starting from **116**, reaction time 23 h) and chromatography on silica gel (hexane:EtOAc, from 2:1 to 1:1) to afford **112** (17 mg, 99%) as a white solid.

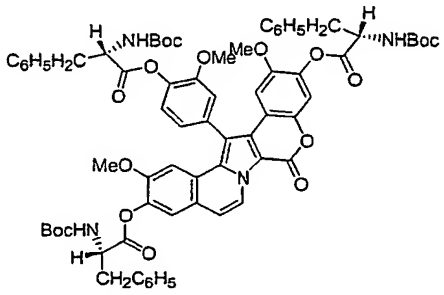
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.11 (d, J= 7.5 Hz, 1H), 7.50-7.00 (m, 20H), 6.78 (s, 1H), 6.71 (d, J= 7.5 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.47 (s, 3H), 3.40 (s, 3H), 3.20-2.80 (m, 12H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 170.7, 155.0, 153.1, 152.3, 147.7, 145.4, 141.8, 140.2, 140.1, 140.0, 139.9, 139.7, 138.9, 134.2, 133.2, 128.7, 128.6, 128.5, 128.4, 128.3, 126.7, 126.5, 126.4, 124.0, 123.3, 123.2, 120.9, 118.2, 115.6, 115.0, 112.1, 108.9, 106.5, 106.1, 104.1, 60.8, 56.2, 55.7, 55.6, 35.5 (3C), 31.0, 30.9, 30.8.

MS (ESI) m/z: 948 $(M+23)^+$, 926 $(M+1)^+$.

Rf: 0.39 (hexane:EtOAc, 2:1).

Compound **113**



General procedure **E** (starting from **121**, reaction time 22 h) and chromatography on silica gel (CH_2Cl_2:MeOH, 80:1) to afford **113** (43 mg, 86%) as a white solid.

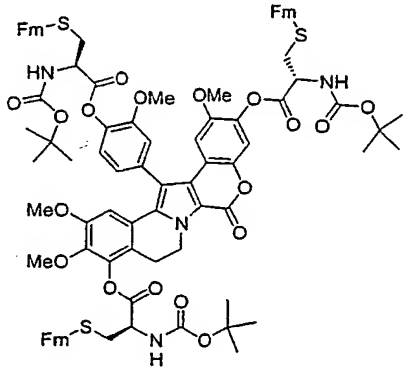
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (d, J= 7.3 Hz, 1H), 7.37-7.20 (m, 20H), 7.08-7.03 (m, 2H), 6.80 (d, J= 2.2 Hz, 1H), 5.29-5.02 (m, 3H), 4.90-4.88 (m, 3H), 3.85 (s, 3H), 3.44 (s, 6H), 3.41-3.23 (m, 6H), 1.46 (s, 9H), 1.43 (s, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 170.0, 169.9, 155.1 (2C), 154.9, 152.3, 150.9, 147.6, 145.3, 140.5, 139.9, 139.3, 135.8 (2C), 134.5, 133.4, 125.0 (9C), 128.6 (6C), 128.1, 128.0, 127.1 (2C), 124.0, 123.7, 123.6, 123.1, 120.7, 115.8, 115.1, 112.8, 112.3, 112.1, 109.1, 106.4, 106.1, 80.1 (3C), 56.2 (2C), 55.7, 55.6, 55.5, 54.4, 38.1 (3C), 28.2 (9C).

MS (ESI) m/z: 1263 $(M+23)^+$, 1241 $(M+1)^+$.

Rf: 0.56 (CH_2Cl_2:MeOH, 50:1).

Compound **114**



General procedure **D** (starting from **1** and (L)-N-Boc-Cys(Fm)) and chromatography on silica gel (hexane:EtOAc, 1:1) to afford **114** as a white solid (140 mg, 88%).

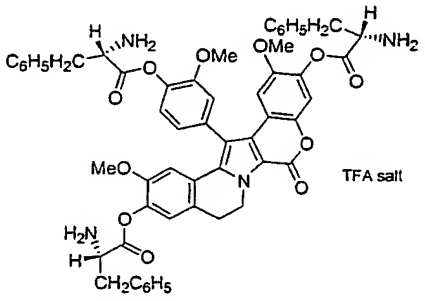
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.65 (m, 12H), 7.45-7.25 (m, 12H), 7.25-7.05 (m, 4H), 6.64 (t, J = 2.9 Hz, 2H), 5.50-5.30 (m, 3H), 4.90-4.70 (m, 4H), 4.60 (br s, 1H), 4.25-4.10 (m, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 3.35 (s, 3H), 3.33 (s, 3H), 3.30-3.10 (m, 12H), 2.95 (m, 2H), 1.48 (s, 18H), 1.46 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 169.1, 155.1, 154.9, 151.9, 151.7, 147.4, 145.7, 145.5, 144.8, 141.1, 141.0, 140.9, 139.5, 138.4, 134.7, 134.4, 127.7, 127.6, 127.5, 127.0, 126.9, 124.8, 124.7, 124.6, 123.7, 123.2, 122.6, 120.0, 119.9, 119.8, 119.3, 116.2, 115.6, 114.8, 114.7, 111.9, 107.7, 105.4, 80.5, 80.4, 80.3, 60.8, 56.1, 55.6, 55.5, 53.6, 53.4, 46.9, 41.9, 37.3, 37.2, 37.1, 35.6, 35.2, 31.9, 29.6, 28.3, 22.2.

MS (ESI) m/z: 1698 $(M+23)^+$, 1676 $(M+1)^+$.

Rf: 0.19 (hexane:EtOAc, 2:1).

Compound **115**

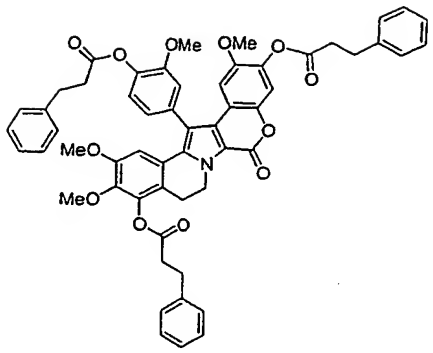


General procedure **B** (starting from **121**) to afford **115** as a white solid (17 mg, quant.).

^1H NMR (300 MHz, CD_3OD) δ 7.44-7.35 (m, 17H), 7.26 (d, J= 8.1 Hz, 1H), 7.10 (d, J= 1.6 Hz, 1H), 7.06 (s, 1H), 6.88 (d, J= 3.5 Hz, 1H), 6.78 (d, J= 3.5 Hz, 1H), 4.79-4.70 (m, 3H), 4.63 (t, J= 6.7 Hz, 2H), 3.89 (s, 3H), 3.53-3.26 (m, 6H), 3.44 (s, 3H), 3.36 (s, 3H), 3.16 (t, J= 6.7 Hz, 2H).

MS (ESI) m/z: 965 $(M+23)^+$, 943 $(M+1)^+$.

Compound **116**



General procedure **F** (starting from **1** and hydrocinnamoyl chloride) and chromatography on silica gel (hexane:EtOAc, from 2:1 to 1:1) to afford **116** as a white solid (32 mg, 74%).

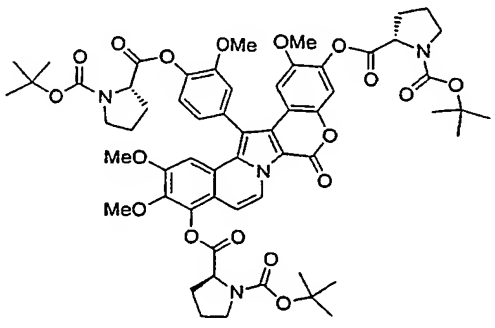
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.20 (m, 15H), 7.15-7.05 (m, 3H), 7.02 (s, 1H), 6.66 (s, 2H), 4.80-4.70 (m, 1H), 4.70-4.50 (m, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.39 (s, 3H), 3.38 (s, 3H), 3.20-2.80 (m, 12H), 2.71 (t, J= 6.4 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 170.7, 170.6, 155.0, 152.2, 151.8, 147.6, 144.9, 141.5, 141.1, 140.2, 140.1, 140.0, 139.9, 138.9, 134.8, 134.0, 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 127.1, 126.6, 126.4, 126.3, 123.8, 123.2, 122.5, 119.1, 115.9, 115.7, 114.7, 114.6, 111.8, 107.5, 105.4, 60.7, 56.2, 55.7, 55.5, 41.8, 35.5, 35.4, 35.3, 30.9, 30.8, 30.8, 21.9.

MS (ESI) m/z: 950 $(M+23)^+$, 928 $(M+1)^+$.

Rf: 0.37 (hexane:EtOAc, 2:1).

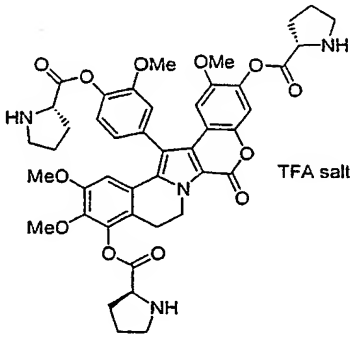
Compound **117**



General procedure **E** (starting from **124**, reaction time 31 h) and chromatography on silica gel (CH_2Cl_2:MeOH, from 50:1 to 30:1) to afford **117** as a brownish solid (40 mg, 67%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.21 (d, J= 7.3 Hz, 1H), 7.50-7.00 (m, 6H), 6.85-6.70 (m, 1H), 4.80-4,40 (m, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 3.75-3.50 (m, 6H), 3.47 (s, 3H), 3.42 (s, 3H), 2.50-2.20 (m, 6H), 2.20-1.85 (m, 6H), 1.52 (s, 9H), 1.49 (s, 9H), 1.47 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 170.9, 170.8, 155.0, 154.6, 154.4, 154.3, 153.8, 153.7, 152.4, 147.7, 145.5, 141.6, 140.1, 139.7, 134.4, 133.2, 124.2, 123.6, 123.4, 123.2, 121.0, 118.7, 115.7, 115.2, 112.3, 111.9, 107.5, 106.6, 106.1, 104.1, 80.2, 80.1, 79.9, 60.7, 59.0, 58.9, 56.1, 55.8, 55.7, 55.5, 46.6, 46.5, 46.4, 28.5, 28.4, 28.2, 24.5, 24.4, 24.3, 23.6, 23.5, 23.4.
MS (ESI) m/z: 1143 $(M+23)^+$.
Rf: 0.32 (CH_2Cl_2:MeOH, 50:1).

Compound **118**

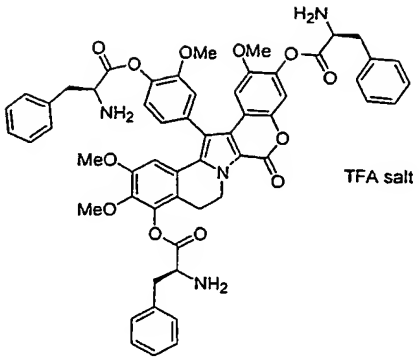


General procedure **B** (starting from **124**) to afford **118** as a white solid (25 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 7.49 (d, J= 7.8 Hz, 1H), 7.41 (s, 1H), 7.30-7.20 (m, 2H), 6.81 (d, J= 7.9 Hz, 1H), 6.76 (d, J= 9.7 Hz, 1H), 4.90-4.70 (m, 5H), 3.87 (s, 3H), 3.81 (s, 3H), 3.60-3.40 (m, 12H), 3.08 (br t, 2H), 2.70-2.30 (m, 6H), 2.30-2.00 (m, 6H).

MS (ESI) m/z: 823 $(M+1)^+$.

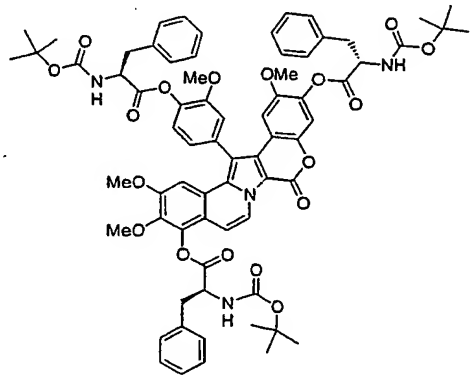
Compound **119**



General procedure **B** (starting from **125**) to afford **119** as a white solid (28 mg, 99%).

^{1}H NMR (300 MHz, CD_3OD) δ 7.50-7.35 (m, 16H), 7.30-7.20 (m, 2H), 7.15-7.10 (m, 1H), 6.82-6.75 (m, 2H), 4.85-4.55 (m, 5H), 3.88 (s, 3H), 3.81 (s, 3H), 3.60-3.40 (m, 12H), 2.94 (br s, 2H).
MS (ESI) m/z: 973 $(M)^+$.

Compound **120**



General procedure **E** (starting from **125**, reaction time 31 h) and chromatography on silica gel (CH_2Cl_2:MeOH, 50:1) to afford **120** as a yellow solid (54 mg, 80%).

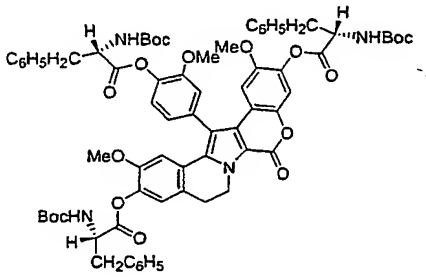
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.12 (dd, J= 7.5, 2.5 Hz, 1H), 7.40-7.20 (m, 19H), 7.10-7.00 (m, 2H), 6.79 (d, J= 4.0 Hz, 1H), 5.20-4.80 (m, 6H), 3.86 (s, 3H), 3.85 (s, 3H), 3.48 (s, 3H), 3.44 (s, 3H), 3.40-3.20 (m, 6H), 1.46 (s, 18H), 1.43 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 170.0, 169.8, 155.3, 155.1, 155.0, 154.8, 153.1, 152.2, 147.5, 145.3 (2C), 141.7, 139.8, 139.2 (2C), 138.8, 135.8, 135.7, 135.6, 134.6, 133.1 (2C), 129.5 (3C), 129.4 (3C), 128.8 (2C), 128.6 (2C), 128.1, 127.3, 127.2, 123.9, 123.6, 123.3, 120.9, 118.2, 115.8, 115.1, 112.0, 108.9, 106.9, 106.1, 104.2, 80.4, 80.2, 80.0, 60.8, 56.2, 56.1, 55.7, 54.7, 54.3 (2C), 38.1 (2C), 37.8, 28.2 (9C).

MS (ESI) m/z: 1293 $(M+23)^+$.

Rf: 0.32 (CH_2Cl_2:MeOH, 60:1).

Compound **121**



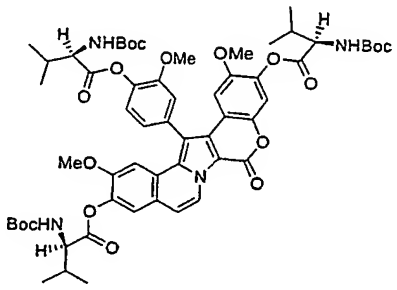
General procedure **D** (starting from **109** and Boc-L-Phe-OH) and chromatography on silica gel (CH_2Cl_2:MeOH, 100:1) to afford **121** as a white solid (87 mg, 68%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.26 (m, 15H), 7.16 (br s, 2H), 7.10 (s, 1H), 7.05 (s, 1H), 6.91 (s, 1H), 6.78-6.68 (m, 2H), 4.99 (t, J= 8.6 Hz, 2H), 4.88-4.72 (m, 6H), 3.81 (s, 3H), 3.41 (s, 3H), 3.34 (s, 3H), 3.30-3.12 (m, 8H), 1.44 (s, 9H), 1.43 (s, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 169.9 (2C), 155.0, 154.9, 152.0, 149.7, 147.5, 144.7, 139.6, 139.0, 138.4, 135.8 (2C), 134.8, 134.2, 129.4 (9C), 129.2, 128.5 (6C), 127.1 (2C), 126.9, 125.9, 125.7, 123.8,

123.1, 122.5, 116.1, 115.8, 114.9, 114.7, 111.8, 109.7, 105.4, 80.0 (3C), 56.1, 55.6, 55.4, 54.3 (3C), 42.3, 38.0 (3C), 28.2 (9C), 27.9.
MS (ESI) m/z: 1265 $(M+23)^+$.
Rf: 0.65 (CH_2Cl_2:MeOH, 30:1).

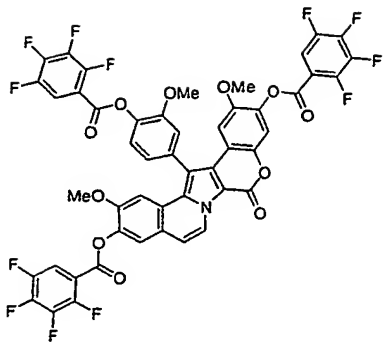
Compound **122**



General procedure **E** (starting from **134**, reaction time 22 h) and chromatography on silica gel (CH_2Cl_2:MeOH, 50:1) to afford **122** (47 mg, 94%) as a white solid.

^1H NMR (300 MHz, $CDCl_3$) δ 9.26 (d, J= 7.3 Hz, 1H), 7.42 (s, 1H), 7.31-7.26 (m, 2H), 7.23-7.18 (m, 3H), 7.09 (d, J= 7.5 Hz, 1H), 6.80 (d, J= 7.5 Hz, 1H), 5.09-5.06 (m, 3H), 4.57-4.50 (m, 3H), 3.80 (s, 3H), 3.43 (s, 6H), 2.45-2.34 (m, 3H), 1.50 (s, 9H), 1.47 (s, 18H), 1.14-1.00 (m, 18H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4 (b), 155.7, 154.9, 152.3, 150.9, 147.6, 145.4, 140.6, 140.0, 139.4, 134.5, 133.4, 128.1, 124.0, 123.8, 123.6, 123.1, 120.8, 115.8, 115.1, 112.8, 112.2, 112.2, 109.1, 106.4, 106.1, 80.0 (3C), 58.5 (2C), 56.0, 55.6, 55.5, 55.4, 30.0 (3C), 28.3 (9C), 19.2, 19.1 (2C), 17.2, 17.1 (2C).
MS (ESI) m/z: 1119 $(M+23)^+$, 1097 $(M+1)^+$.
Rf: 0.33 (CH_2Cl_2:MeOH, 100:1).

Compound **123**



General procedure **E** (starting from **139**, reaction time 7 h) and chromatography on silica gel (CH_2Cl_2:MeOH, 100:1) to afford **123** (15 mg, 75%) as a white solid.

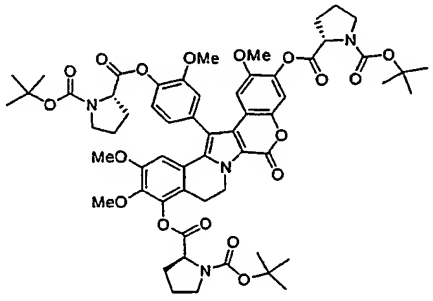
^1H NMR (300 MHz, $CDCl_3$) δ 9.24 (d, J= 7.5 Hz, 1H), 7.84-7.75 (m, 3H), 7.54 (s, 1H), 7.45 (d, J= 8.4 Hz, 1H), 7.37-7.35 (m, 2H), 7.30 (s, 1H), 7.26 (s, 1H), 7.08 (d, J= 7.3 Hz, 1H), 6.90 (s, 1H), 3.87 (s, 3H), 3.52 (s, 3H), 3.52 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7 (3C), 154.8, 152.3, 150.8, 148.2, 147.6, 145.4, 140.3, 139.8, 139.2, 135.0, 133.4, 128.0, 124.0, 123.9, 123.8, 123.7, 123.2, 120.7, 116.2, 115.3, 113.8, 113.6, 112.8, 112.4, 112.1, 109.2, 106.6, 106.3, 56.4, 55.9, 55.8.

MS (ESI) m/z: 1050 $(M+23)^+$, 1028 $(M+1)^+$.

Rf: 0.63 (CH_2Cl_2).

Compound **124**



General procedure **D** (starting from **1** and (L)-N-Boc-Pro) and chromatography on silica gel (CH_2Cl_2:MeOH, from 50:1 to 20:1) to give **124** as a white solid (105 mg, 99%).

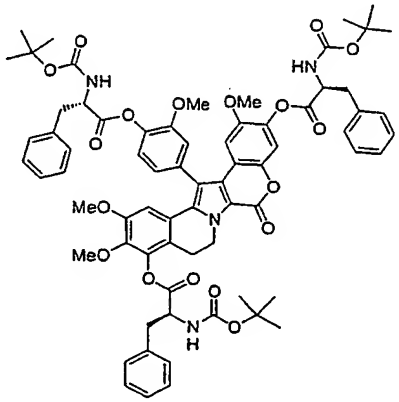
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.10 (m, 2H), 7.10-7.00 (m, 2H), 6.70-6.60 (m, 2H), 4.90 (br s, 1H), 4.70-4.40 (m, 4H), 3.78 (s, 6H), 3.70-3.40 (m, 6H), 3.39 (s, 3H), 3.36 (s, 3H), 3.20-2.95 (m, 2H), 2.50-2.20 (m, 6H), 2.15-1.85 (m, 6H), 1.48 (s, 18H), 1.46 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 170.9, 170.7, 155.0, 154.4, 153.8, 152.2, 151.7, 147.6, 144.8, 141.4, 141.0, 139.8, 138.7, 134.3, 127.1, 124.0, 123.4, 123.2, 122.6, 119.9, 119.0, 116.0, 115.7, 114.7, 112.1, 111.6, 107.5, 105.4, 80.2, 80.0, 79.9, 60.6, 58.9, 58.8, 56.1, 55.7, 55.6, 55.5, 46.6, 46.5, 46.4, 42.0, 28.3, 24.4, 24.3, 23.6, 23.5, 23.4, 23.3, 22.0.

MS (ESI) m/z: 1145 $(M+23)^+$, 1124 $(M+1)^+$.

Rf: 0.64 (CH_2Cl_2:MeOH, 20:1).

Compound **125**

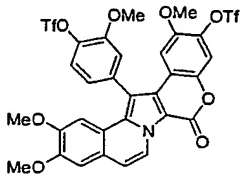


General procedure **D** (starting from **1** and (L)-Boc-Phe) and chromatography on silica gel (CH_2Cl_2:MeOH, from 50:1 to 30:1) to afford **125** as a brown solid (119 mg, 99%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.25 (m, 15H), 7.20-7.10 (m, 3H), 7.03 (s, 1H), 5.10-5.00 (m, 3H), 5.00-4.80 (m, 3H), 4.75-4.50 (m, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.78 (s, 6H), 3.40 (s, 3H), 3.37 (s, 3H), 3.35-3.00 (m, 6H), 2.95-2.85 (m, 2H), 1.44 (s, 9H), 1.43 (s, 9H), 1.42 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 169.9 (2C), 155.2, 154.9, 152.1, 151.8, 147.5, 144.8, 141.3, 141.0, 139.6, 138.4, 135.8, 135.6, 134.7, 134.3, 129.5 (3C), 129.4 (2C), 129.2 (2C), 128.7 (2C), 128.5 (2C), 128.4 (2C), 127.2, 127.1, 126.9, 123.7, 123.2, 122.6, 119.4, 116.2, 115.6, 114.8, 114.7, 111.8, 107.6, 105.4, 80.3, 80.1, 80.0, 60.7, 56.1, 55.6, 55.5, 54.3, 53.4, 52.1, 41.8, 38.1 (2C), 37.8, 28.2 (9C), 22.0.
MS (ESI) m/z: 1295 $(M+23)^+$, 1273 $(M+1)^+$.
Rf: 0.21 (CH_2Cl_2:MeOH, 50:1).

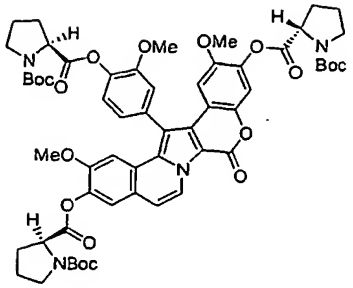
Compound **126**



General procedure **I** (starting from **26**) and chromatography on silica gel (CH_2Cl_2) to afford **126** as a pale yellow solid (24.2 mg, quant.).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.16 (d, J= 7.3 Hz, 1H), 7.54 (d, J= 8.1 Hz, 1H), 7.40-7.25 (m, 2H), 7.20 (s, 1H), 7.11 (br s, 2H), 6.98 (s, 1H), 6.76 (s, 1H), 3.99 (s, 3H), 3.98 (s, 3H), 3.50 (s, 3H), 3.46 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 152.6, 150.7, 149.8, 147.9, 144.9, 138.8, 137.7, 137.4, 134.3, 129.6, 127.5, 127.2, 125.0, 124.1, 123.7, 122.9, 118.6 (2C, t, J_{C-F}=172.7, 164.5 Hz), 116.3, 113.7, 112.0, 110.2, 107.7, 106.5, 104.7, 56.7, 56.0, 55.8, 55.2.
MS (ESI) m/z: 778 $(M+1)^+$.
Rf: 0.36 (CH_2Cl_2).

Compound **127**



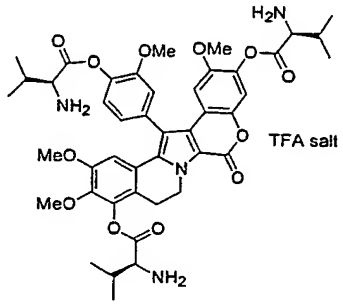
General procedure **E** (starting from **140**, reaction time 17 h) and chromatography on silica gel (CH_2Cl_2:MeOH, 30:1) to afford **127** (30 mg, 67%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.27-9.23 (m, 1H), 7.47-7.36 (m, 1H), 7.26-7.08 (m, 6H), 6.84-6.78 (m, 1H), 4.56-4.49 (m, 3H), 3.80 (s, 3H), 3.66-3.47 (m, 6H), 3.43 (s, 6H), 2.40-2.29 (m, 6H), 2.04-1.98 (m, 6H), 1.49 (s, 27H).

MS (ESI) m/z: 1091 $(M+1)^+$.

Rf: 0.31 (CH_2Cl_2:MeOH 30:1).

Compound **128**

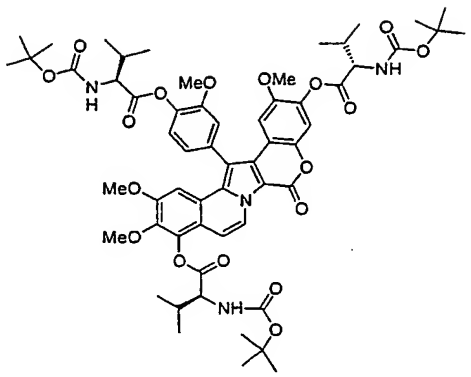


General procedure **B** (starting from **131**) to afford **128** as a white solid (25 mg, 99%).

^{1}H NMR (300 MHz, CD_3OD) δ 7.50-7.40 (m, 2H), 7.30-7.20 (m, 2H), 6.82 (d, J= 5.4 Hz, 1H), 6.79 (d, J= 7.9 Hz, 1H), 4.90-4.70 (m, 2H), 4.44 (d, J= 3.4 Hz, 1H), 4.32 (dd, J= 4.2, 1.6 Hz, 1H), 4.24 (d, J= 4.3 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.44 (s, 3H), 3.43 (s, 3H), 3.15-3.00 (m, 2H), 2.65-2.40 (m, 3H), 1.30-1.15 (m, 18H).

MS (ESI) m/z: 851 $(M+23)^+$, 829 $(M+1)^+$.

Compound **129**



General procedure **E** (starting from **131**, reaction time 24 h) and chromatography on silica gel (CH_2Cl_2:MeOH, from 50:1 to 30:1) to afford **129** as a yellow solid (53 mg, 79%).

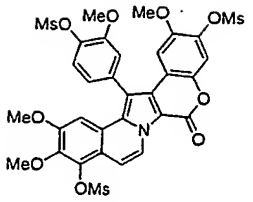
^1H NMR (300 MHz, $CDCl_3$) δ 9.21 (d, J= 7.6 Hz, 1H), 7.40-7.05 (m, 6H), 6.78 (d, J= 9.1 Hz, 1H), 5.15-5.05 (m, 3H), 4.65-4.50 (m, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.48 (s, 3H), 3.42 (s, 3H), 2.50-2.30 (m, 3H), 1.49 (s, 18H), 1.46 (s, 9H), 1.25-0.95 (m, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2 (3C), 155.9, 155.7, 154.9, 153.1, 152.2, 147.6, 145.4, 145.3, 141.7, 139.9, 139.4, 138.7, 134.5, 133.1, 128.3 (2C), 124.0, 123.6, 123.5, 121.0, 118.3, 115.8, 115.1, 112.1, 109.0, 106.9, 106.1, 104.2, 80.3, 80.0 (2C), 60.7, 59.0, 58.6 (2C), 56.0, 55.7, 55.6, 31.3, 31.1, 30.9, 28.3 (9C), 19.3, 19.2, 19.0, 17.5, 17.2, 17.1.

MS (ESI) m/z: 1149 $(M+23)^+$.

Rf: 0.19 (CH_2Cl_2:MeOH, 50:1).

Compound **130**



General procedure **E** (starting from **136**, reaction time 3 d) and chromatography on silica gel (CH_2Cl_2:MeOH, from 50:1 to 30:1) to afford **130** as a brownish solid (105 mg, 99%).

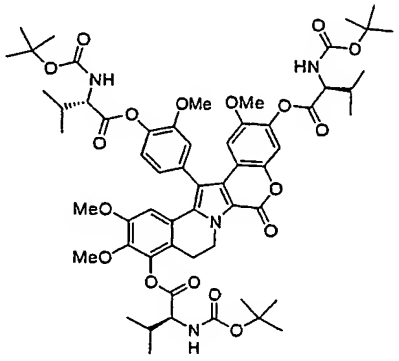
^1H NMR (300 MHz, $CDCl_3$) δ 9.15 (d, J= 7.6 Hz, 1H), 7.59 (d, J= 8.0 Hz, 1H), 7.37 (d, J= 7.5 Hz, 1H), 7.35-7.25 (m, 3H), 7.08 (s, 1H), 6.75 (s, 1H), 3.99 (s, 3H), 3.96 (s, 3H), 3.49 (s, 3H), 3.47 (s, 3H), 3.42 (s, 3H), 3.37 (s, 3H), 3.19 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 153.1, 152.9, 148.0, 145.1, 142.6, 138.3, 138.2, 137.7, 135.7, 132.6, 127.6, 125.8, 123.8, 123.6, 121.0, 119.8, 116.6, 115.7, 113.7, 111.8, 109.1, 107.7, 106.4, 104.9, 61.5, 56.6, 55.8, 55.6, 39.7, 39.3, 38.6.

MS (ESI) m/z: 764 $(M+1)^+$.

Rf: 0.54 (CH_2Cl_2:MeOH, 50:1).

Compound **131**



General procedure **D** (starting from **1** and (L)-Boc-Valine) and chromatography on silica gel (CH_2Cl_2:MeOH, from 50:1 to 30:1) to afford **131** as a yellow solid (105 mg, 99%).

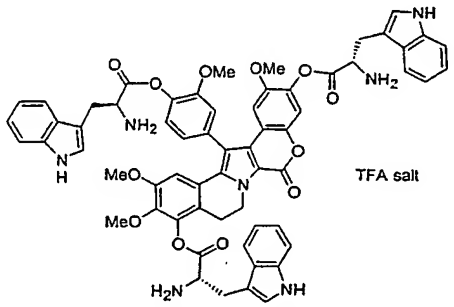
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.10 (m, 2H), 7.08 (s, 2H), 6.63 (t, J= 8.9 Hz, 2H), 5.30-5.10 (m, 3H), 4.70 (br s, 1H), 4.66 (br s, 1H), 4.60-4.45 (m, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.38 (s, 3H), 3.37 (s, 3H), 3.00 (br t, 2H), 2.45-2.30 (m, 3H), 1.48 (s, 9H), 1.47 (s, 9H), 1.45 (s, 9H), 1.15-0.95 (m, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 170.4 (2C), 155.7, 155.6, 154.9, 152.0, 151.8, 147.4, 144.8, 141.2, 141.0, 139.6, 138.5, 134.7, 134.3, 127.0, 126.9, 123.8, 123.2, 122.6, 119.4, 116.1, 115.6, 114.8, 114.7, 111.8, 107.6, 105.4, 80.1, 80.0, 79.9, 60.6, 58.8, 58.5, 58.4, 56.0, 55.6, 55.4, 41.8, 31.3, 31.1, 30.8, 28.3 (9C), 22.2, 19.2, 19.1, 19.0, 17.4, 17.1, 17.0.

MS (ESI) m/z: 1151.7 $(M+23)^+$, 1129.8 $(M+1)^+$.

Rf: 0.70 (CH_2Cl_2:MeOH, 20:1).

Compound **132**

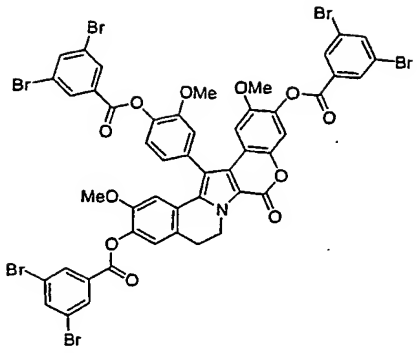


General procedure **B** (starting from **131**) to afford **132** as a brownish solid (50 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 7.90-7.40 (m, 19H), 6.80-6.70 (m, 2H), 4.90-4.50 (m, 5H), 3.90 (s, 3H), 3.79 (s, 3H), 3.60-3.30 (m, 12H), 2.72 (br s, 2H).

MS (ESI) m/z: 1090 $(M)^+$.

Compound **133**



General procedure **D** (starting from **109** and 3,5-dibromobenzoic acid) and chromatography on silica gel (CH_2Cl_2:MeOH, from 200:1 to 100:1) to afford **133** as a white solid (43 mg, 67%).

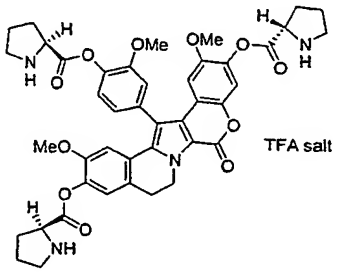
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, J= 1.8 Hz, 2H), 8.26 (d, J= 1.8 Hz, 2H), 8.24 (d, J= 1.8 Hz, 2H), 7.95-7.92 (m, 3H), 7.34 (d, J= 8.1 Hz, 1H), 7.26 (s, 1H), 7.24-7.20 (m, 2H), 7.08 (s, 1H), 6.88 (s, 1H), 6.81 (s, 1H), 4.94-4.89 (m, 1H), 4.81-4.77 (m, 1H), 3.83 (s, 3H), 3.49 (s, 3H), 3.43 (s, 3H), 3.17 (t, J= 6.7 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 154.9, 151.9, 149.1, 147.6, 147.4, 144.7, 139.4, 138.3, 135.8, 134.4, 129.4, 129.2, 128.5, 127.1, 126.4, 126.3, 123.6, 123.3, 119.5, 116.3, 114.9, 114.6, 114.4, 111.7, 110.9, 108.4, 105.4, 79.9,79.9 (2C), 56.0, 55.8, 55.6, 55.4, 54.3 (2C), 42.4, 38.0 (2C), 28.4, 28.2 (6C).

MS (APCI) m/z: 1288 $(M+1)^+$.

Rf: 0.72 (CH_2Cl_2).

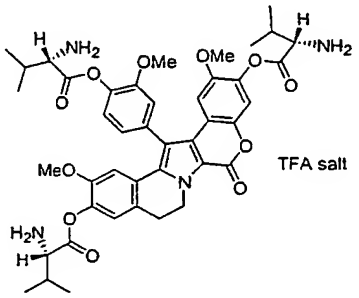
Compound **134**



General procedure **B** (starting from **140**) to afford **134** as a white solid (17 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 7.49-7.44 (m, 2H), 7.29-7.17 (m, 3H), 6.88-6.75 (m, 2H), 4.79-4.68 (m, 3H), 3.89 (s, 3H), 3.52-3.38 (m, 12H), 3.15 (br t, 2H), 2.63-2.35 (m, 6H), 2.25-2.15 (m, 6H).
MS (ESI) m/z: 793 $(M+1)^+$.

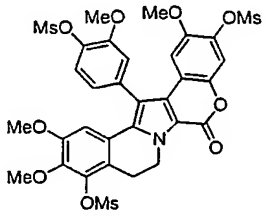
Compound **135**



General procedure **B** (starting from **144**) to afford **135** as a white solid (16 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 7.47-7.44 (m, 2H), 7.28 (d, J= 8.1 Hz, 1H), 7.19 (s, 1H), 7.15 (s, 1H), 6.90-6.78 (m, 2H), 4.77 (br t, 2H), 4.32 (s, 1H), 4.24 (s, 2H), 3.87 (s, 3H), 3.45 (s, 3H), 3.37 (s, 3H), 3.17 (br t, 2H), 2.54-2.46 (m, 3H), 1.26-1.17 (m, 18H).
MS (ESI) m/z: 799 $(M+1)^+$.

Compound **136**



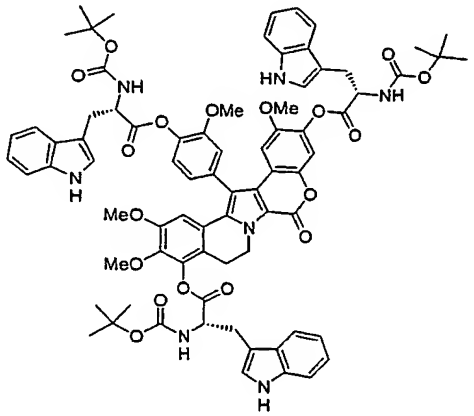
To a solution of **1** (25 mg, 0.047 mmol) in anhydrous CH_2Cl_2 (2 mL) under Argon at 0 °C, Et_3N (39 µL, 0.28 mmol) and methanesulfonyl

chloride (22 μL, 0.28 mmol) were added. The resulting mixture was stirred at 23 °C for 2 h, then quenched with H_2O and extracted with CH_2Cl_2 (3x20 mL).

The combined organic phases were washed with saturated aqueous solution of $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The resulting residue was purified on silica gel (CH_2Cl_2:MeOH, 50:1) to afford **136** as a brownish solid (35 mg, 97%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J= 8.0 Hz, 1H), 7.30-7.15 (m, 3H), 6.66 (s, 1H), 6.63 (s, 1H), 5.00-4.90 (m, 1H), 4.75-4.50 (m, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.45 (s, 3H), 3.37 (s, 3H), 3.35 (s, 3H), 3.32 (s, 3H), 3.30-3.20 (m, 2H), 3.17 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 152.8, 151.9, 148.0, 144.7, 141.8, 141.0, 138.0, 137.0, 135.6, 134.4, 126.3, 125.6, 123.5, 123.1, 121.7, 117.0, 115.5, 115.3, 113.6, 108.2, 105.7, 61.3, 56.5, 55.8, 55.5, 42.0, 39.4, 39.2, 38.6, 23.3. MS (APCI) m/z: 766 $(M+1)^+$.
Rf: 0.54 (CH_2Cl_2:MeOH, 50:1).

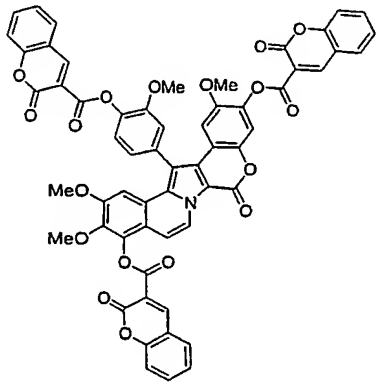
Compound **137**



General procedure **D** (starting from **1** and (L)-N-Boc-Trp) and chromatography on silica gel (CH_2Cl_2:MeOH, from 30:1 to 20:1) to afford **137** as a brown solid (130 mg, 99%).

^1H NMR (300 MHz, $CDCl_3$) δ 8.51 (s, 2H), 8.42 (br s, 1H), 7.70-7.60 (m, 3H), 7.45-7.30 (m, 3H), 7.30-6.95 (m, 9H), 6.87 (s, 1H), 6.70-6.55 (m, 2H), 5.30-5.15 (m, 2H), 5.10-4.90 (m, 3H), 4.80-4.40 (m, 2H), 3.76 (s, 6H), 3.60-3.30 (m, 12H), 2.70 (br s, 2H), 1.45 (s, 27H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 170.4 (2C), 155.2, 154.9, 152.0, 151.7, 147.5, 144.6, 141.4, 141.0, 139.6, 138.5, 136.1 (2C), 134.7, 134.1, 127.7, 127.6, 126.8, 123.8, 123.4, 123.1 (2C), 122.6, 122.2, 119.7, 119.6 (2C), 118.7, 118.6, 116.0, 115.6, 114.6, 111.7, 111.3 (2C), 109.8, 109.4, 107.6, 105.4, 80.2, 80.0 (2C), 60.8, 56.1, 55.6, 55.5, 54.4 (2C), 53.4, 41.7, 28.2 (9C+3C), 21.7.
MS (ESI) m/z: 1412 $(M+23)^+$, 1391 $(M+1)^+$.
Rf: 0.22 (CH_2Cl_2:MeOH, 30:1).

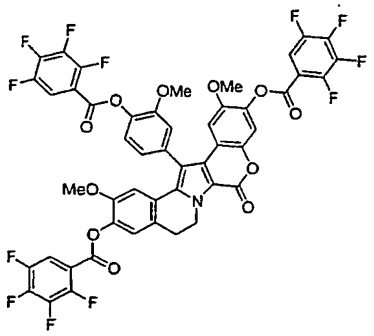
Compound **138**



General procedure **E** (starting from **149**, reaction time 2 d) and chromatography on silica gel (CH_2Cl_2:MeOH, from 100:1 to 50:1) to afford **138** as a white solid (29 mg, 83%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (d, J= 7.6 Hz, 1H), 8.85 (d, J= 4.5 Hz, 2H), 8.78 (s, 1H), 7.80-7.60 (m, 6H), 7.55-7.20 (m, 11H), 7.18 (s, 1H), 6.89 (s, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 3.60 (s, 3H), 3.53 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2, 160.6, 160.3, 156.4, 156.2, 155.5, 155.4, 155.3, 154.8, 153.3, 152.4, 150.5, 150.4, 150.1, 147.7, 145.4, 141.8, 139.9, 139.4, 138.7, 135.1, 135.0, 134.9, 134.7, 133.2, 129.9, 129.8, 129.7, 128.2, 125.1, 125.0, 124.9, 124.1, 123.7, 123.4, 120.9, 118.2, 117.8, 117.7, 117.7, 116.9, 116.7, 116.5, 115.9, 115.4, 112.3, 112.1, 109.0, 106.9, 106.3, 104.4, 61.0, 56.4, 56.1, 55.9.
MS (ESI) m/z: 1046 $(M+1)^+$.
Rf: 0.50 (CH_2Cl_2:MeOH, 50:1).

Compound **139**

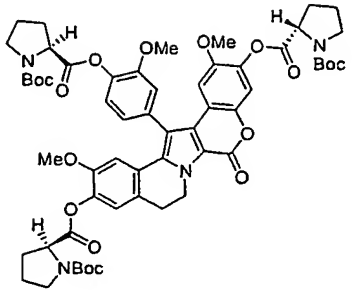


General procedure **D** (starting from **1** and 2,3,4,5-tetrafluorobenzoic acid) and chromatography on silica gel (CH_2Cl_2:MeOH, 200:1) to afford **139** as a white solid (33 mg, 64%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81-7.74 (m, 3H), 7.36 (d, J= 8.1 Hz, 1H), 7.25 (s, 1H), 7.23 (s, 1H), 7.19 (s, 1H), 7.10 (s, 1H), 6.86 (s, 1H), 6.78 (s, 1H), 4.97-4.91 (m, 1H), 4.82-4.77 (m, 1H), 3.83 (s, 3H), 3.48 (s, 3H), 3.41 (s, 3H), 3.17 (t, J= 6.5 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6 (3C), 154.9, 152.1, 149.7, 147.5, 144.9, 139.5, 138.9, 138.3, 134.9, 134.7, 126.9, 126.2, 126.1, 123.7, 123.3, 122.5, 116.5, 115.9, 115.2, 114.9, 113.8, 113.5, 111.9, 109.9, 105.6, 56.3, 55.9, 55.7, 42.5, 28.1. MS (APCI) m/z: 1030 $(M+1)^+$.

Rf: 0.50 (CH_2Cl_2:MeOH, 200:1).

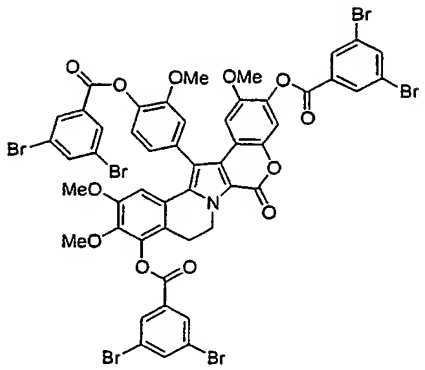
Compound **140**



General procedure **D** (starting from **109** and Boc-L-Pro-OH) and chromatography on silica gel (CH_2Cl_2:MeOH, from 100:1 to 50:1) to afford **140** as a white solid (74 mg, 68%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16-7.13 (m, 2H), 7.06-7.03 (m, 2H), 6.90 (s, 1H), 6.78-6.63 (m, 2H), 4.95-4.62 (m, 2H), 4.56-4.46 (m, 3H), 3.78 (s, 3H), 3.69-3.43 (m, 6H), 3.40 (s, 3H), 3.33 (s, 3H), 3.11 (br t, 2H), 2.40-2.26 (m, 6H), 2.08-1.90 (m, 6H), 1.47 (s, 27H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 170.8, 170.7, 155.0, 154.3, 153.7, 153.7 (2C), 152.1, 149.7, 147.6, 144.8, 139.8, 139.3, 138.7, 134.1, 125.9, 125.6, 124.0, 123.4, 123.1 (2C), 122.7, 122.2, 116.0, 114.7, 111.6, 109.6, 105.3, 80.1, 80.0, 79.8, 58.9 (2C), 56.1, 55.7, 55.6, 55.5, 46.5, 46.3 (2C), 42.4, 31.5, 30.9, 29.9, 28.3 (9C), 28.0, 24.2, 23.4, 22.5.
MS (ESI) m/z: 1115 $(M+23)^+$, 1093 $(M+1)^+$.
Rf: 0.18 (CH_2Cl_2:MeOH, 50:1).

Compound **141**



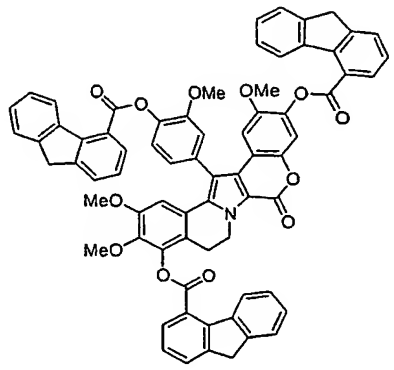
General procedure **D** (starting from **1** and 3,5-dibromobenzoic acid) and chromatography on silica gel (CH_2Cl_2:MeOH, 200:1) to afford **141** as a white solid (61 mg, 98%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, J= 1.7 Hz, 2H), 8.30 (d, J= 1.8 Hz, 2H), 8.26 (d, J= 1.7 Hz, 2H), 7.98 (t, J= 1.7 Hz, 1H), 7.96 (t, J= 1.7 Hz, 1H), 7.93 (t, J= 1.8 Hz, 1H), 7.36 (d, J= 7.8 Hz, 1H), 7.25-7.19 (m, 3H), 6.78 (s, 1H), 6.77 (s, 1H), 5.00-4.60 (br s, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.48 (s, 6H), 3.10-3.00 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 152.5, 152.2, 147.9, 145.2, 141.6, 140.0, 139.5, 139.2, 138.9, 135.1, 134.8, 132.5, 132.2, 129.1, 127.3, 124.0, 123.7, 123.6, 123.5, 123.4, 123.0, 119.3, 116.7, 116.0, 115.1, 112.2, 108.1, 105.8, 61.2, 56.5, 56.1, 55.9, 42.2, 22.6. MS (APCI) m/z: 1319 $(M+1)^+$.

Rf: 0.58 (CH_2Cl_2).

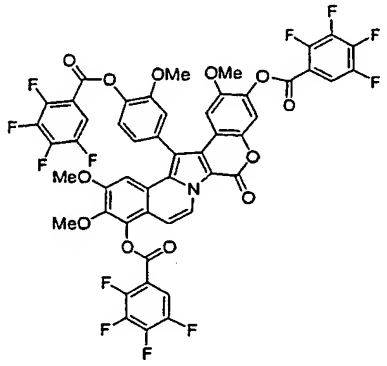
Compound **142**



General procedure **K** (starting from **1** and 4-fluorenecarboxylic acid) and chromatography on silica gel (CH_2Cl_2:MeOH, from 200:1 to 100:1) to afford **142** as a white solid (36 mg, 69%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60-8.40 (m, 3H), 8.30-8.10 (m, 3H), 7.90-7.70 (m, 3H), 7.65-7.55 (m, 3H), 7.55-7.25 (m, 13H), 6.92 (s, 1H), 6.91 (s, 1H), 5.10-4.70 (br s, 2H), 4.00 (s, 2H), 3.99 (s, 2H), 3.96 (s, 2H), 3.93 (s, 3H), 3.91 (s, 3H), 3.60 (s, 3H), 3.58 (s, 3H), 3.18 (br s, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 165.9, 155.1, 152.6, 152.1, 148.0, 145.4. 145.2, 145.1, 145.0, 144.3, 144.2, 144.1, 141.9, 141.8, 141.5, 141.3, 140.4, 140.0, 139.9, 139.8, 139.2, 135.0, 134.3, 129.5, 129.4, 129.3, 129.0, 127.8, 127.7, 127.6, 127.3, 127.0, 126.8, 126.7, 126.2, 126.1, 126.0, 125.4, 125.3, 125.1, 125.0, 124.7, 124.5, 124.1, 123.5, 122.9, 119.6, 116.2, 116.0, 114.9, 112.1, 107.7, 105.6, 61.0, 56.3, 55.8, 55.7, 42.0, 37.0 (3C), 22.5. MS (APCI) m/z: 1108 $(M)^+$.
Rf: 0.34 (CH_2Cl_2).

Compound **143**



General procedure **E** (starting from **99**, reaction time 63 h) and chromatography on silica gel (CH_2Cl_2:MeOH, 200:1) to afford **143** as a white solid (27 mg, 93%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (d, J= 7.5 Hz, 1H), 7.95-7.70 (m, 3H), 7.46 (d, J= 8.2 Hz, 1H), 7.40-7.35 (m, 2H), 7.25 (s, 1H), 7.18 (s, 1H),

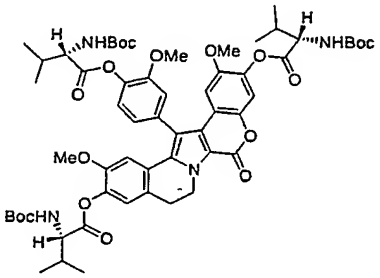
7.11 (d, *J*= 7.6 Hz, 1H), 6.88 (s, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.58 (s, 3H), 3.51 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 153.3, 152.3, 147.6, 145.4, 143.1, 141.7, 139.7, 139.2, 138.5, 135.0, 133.1, 128.2, 123.9, 123.7, 123.6, 120.9, 117.9, 116.1, 115.3, 113.8, 112.1, 109.1, 106.4, 106.3, 104.6, 61.0, 56.4, 55.9, 55.7.

MS (APCI) m/z: 1058 $(M+1)^+$.

Rf: 0.54 (CH_2Cl_2).

Compound **144**



General procedure **D** (starting from **109** and Boc-L-Val-OH) and chromatography on silica gel (CH_2Cl_2:MeOH, from 100:1 to 50:1) to afford **144** as a white solid (87 mg, 79%).

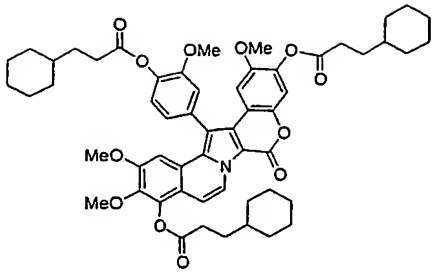
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.13 (m, 2H), 7.09 (s, 2H), 6.96 (s, 1H), 6.76 (d, *J*= 7.5 Hz, 1H), 6.68 (d, *J*= 9.5 Hz, 1H), 5.08-5.05 (m, 3H), 4.91-4.69 (m, 2H), 4.52-4.46 (m, 3H), 3.77 (s, 3H), 3.40 (s, 3H), 3.32 (s, 3H), 3.18 (br t, 2H), 2.42-2.38 (m, 3H), 1.48 (s, 9H), 1.45 (s, 18H), 1.11-0.98 (m, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3 (3C), 155.6, 154.9, 152.1, 149.7, 147.5, 144.8, 139.7, 139.1, 138.5, 134.9, 134.2, 126.9, 126.0, 125.7, 123.8, 123.1, 122.5, 116.1, 115.8, 115.0, 114.6, 111.9, 109.6, 105.4, 79.9 (3C), 58.5, 56.0, 55.6, 55.3, 55.3, 53.4, 42.4, 31.2 (3C), 28.3 (9C), 28.0, 19.1 (2C), 17.1 (4C).

MS (ESI) m/z: 1121 $(M+23)^+$, 1099 $(M+1)^+$.

Rf: 0.35 (CH_2Cl_2:MeOH, 50:1).

Compound **145**



General procedure **E** (starting from **148**, reaction time 24 h) and chromatography on silica gel (CH_2Cl_2:MeOH, 200:1) to afford **145** as a white solid (27 mg, 87%).

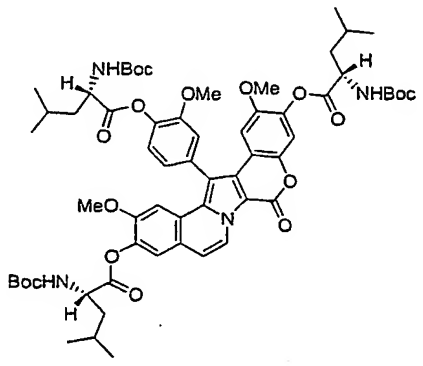
^1H NMR (300 MHz, $CDCl_3$) δ 9.22 (d, J= 7.5 Hz, 1H), 7.35-7.00 (m, 6H), 6.81 (s, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.49 (s, 3H), 3.45 (s, 3H), 2.76 (t, J= 7.6 Hz, 2H), 2.70-2.55 (m, 4H), 1.90-1.60 (m, 18H), 1.50-1.10 (m, 15H), 1.05-0.80 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 171.9, 171.8, 155.0, 153.2, 152.4, 147.8, 145.5, 141.8, 140.4, 139.9, 139.1, 134.1, 133.3, 128.4, 124.1, 123.6, 123.3, 121.0, 118.3, 116.5, 115.5, 115.0, 112.2, 108.9, 106.6, 106.1, 104.0, 60.8, 56.2, 55.7, 55.6, 37.2, 37.1, 37.0, 33.0 (4C), 32.9 (4C), 32.4, 32.3, 32.2, 31.6, 31.5, 26.5, 26.2 (6C).

MS (ESI) m/z: 944 $(M)^+$.

Rf: 0.35 (CH_2Cl_2).

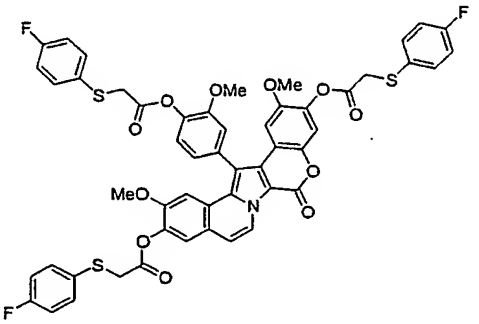
Compound **146**



General procedure **E** (starting from **153**, reaction time 35 h) and chromatography on silica gel (CH_2Cl_2:MeOH, 100:1) to afford **146** (38 mg, 73%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (d, J= 7.3 Hz, 1H), 7.42 (s, 1H), 7.32 (d, J= 7.9 Hz, 1H), 7.25-7.17 (m, 4H), 7.05 (d, J= 7.7 Hz, 1H), 6.79 (d, J= 5.9 Hz, 1H), 4.98-4.96 (m, 3H), 4.62-4.56 (m, 3H), 3.80 (s, 3H), 3.44 (s, 3H), 3.43 (s, 3H), 1.87-1.64 (m, 9H), 1.49 (s, 9H), 1.46 (s, 18H), 1.06-0.99 (m, 18H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4 (4C), 155.3, 155.0, 152.3, 150.9, 147.7, 145.4, 140.7, 140.1, 139.6, 134.4, 128.1, 124.0, 123.8, 123.6, 123.2, 120.7, 115.8, 115.1, 112.8, 112.3, 112.2, 109.1, 106.4, 106.2, 80.0 (3C), 56.2 (2C), 55.8 (2C), 55.7, 52.2, 41.7 (2C), 41.5, 28.3 (9C), 24.8 (3C), 23.0, 22.9 (3C), 21.9.
MS (ESI) m/z: 1161 $(M+23)^+$, 1139 $(M+1)^+$.
Rf: 0.45 (CH_2Cl_2:MeOH, 50:1).

Compound **147**

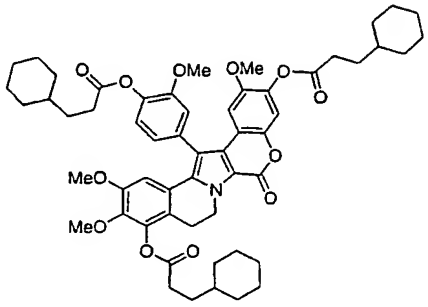


General procedure **E** (starting from **152**, reaction time 40 h) and chromatography on silica gel (CH_2Cl_2:MeOH, from 200:1 to 100:1) to afford **147** (17 mg, 65%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.21 (d, J= 7.3 Hz, 1H), 7.58-7.50 (m, 6H), 7.31 (s, 1H), 7.21-7.16 (m, 4H), 7.10-7.01 (m, 8H), 6.75 (s, 1H), 3.87 (s, 2H), 3.84 (s, 2H), 3.81 (s, 2H), 3.78 (s, 3H), 3.37 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 167.5 (2C), 162.6 (d, J_{C-F}= 248.3, 3C), 154.9, 152.3, 150.8, 147.6, 145.4, 140.6, 140.0, 139.5, 134.6, 133.9, 133.8; 133.8, 133.7, 133.6, 133.4, 129.5, 129.3, 128.1, 123.8, 123.6, 123.2, 120.5, 116.4 (6C), 116.1 (6C), 115.9, 115.1, 112.8, 112.3, 112.0, 109.1, 106.4, 106.2.
MS (ESI) m/z: 1026 $(M+23)^+$, 1004 $(M+1)^+$.
Rf: 0.35 (CH_2Cl_2).

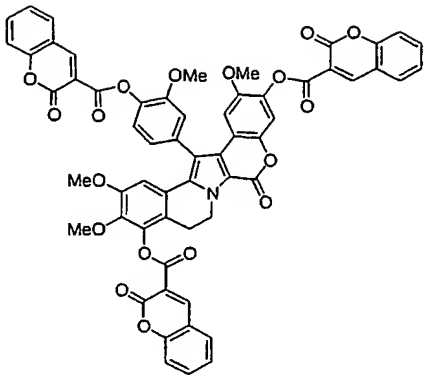
Compound **148**



General procedure **D** (starting from **1** and 3-cyclohexylpropionic acid) and chromatography on silica gel (CH_2Cl_2:MeOH, 100:1) to afford **148** as a white solid (43 mg, 95%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.05 (m, 4H), 6.68 (s, 2H), 5.00-4.80 (m, 1H), 4.80-4.70 (m, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.42 (s, 3H), 3.39 (s, 3H), 3.00-2.90 (m, 2H), 2.70-2.50 (m, 6H), 1.90-1.60 (m, 21H), 1.50-1.10 (m, 12H), 1.05-0.90 (m, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 171.9, 171.8, 155.1, 152.3, 151.8, 147.7, 144.9, 141.6, 141.2, 140.1, 139.1, 134.9, 133.9, 127.2, 123.9, 123.2, 122.6, 119.2, 115.9, 115.8, 114.7, 114.6, 111.9, 107.4, 105.4, 60.7, 56.2, 55.7, 55.5, 41.9, 37.2, 37.1, 37.0, 33.0 (4C), 32.9 (4C), 32.4, 32.3, 32.2, 31.6, 31.5, 31.4, 26.5, 26.3 (2C), 26.2 (2C), 26.1(2C), 22.2.
MS (APCI) m/z: 946 $(M)^+$.
Rf: 0.37 (CH_2Cl_2:MeOH, 100:1).

Compound **149**



General procedure **D** (starting from **1** and coumarin-3-carboxylic acid) and chromatography on silica gel (CH_2Cl_2:MeOH, 50:1) to afford **149** as a white solid (49 mg, 99%).

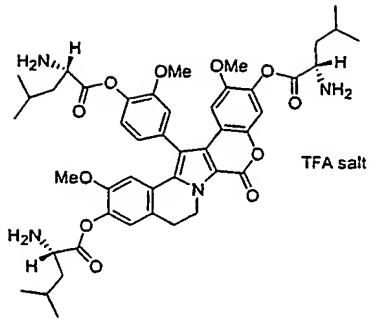
^1H NMR (300 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.80 (s, 1H), 8.77 (s, 1H), 7.80-7.60 (m, 6H), 7.25-7.15 (m, 7H), 7.15-7.05 (m, 3H), 6.78 (s, 1H), 6.76 (s, 1H), 5.00-4.80 (br s, 1H), 4.80-4.60 (br s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.50 (s, 3H), 3.48 (s, 3H), 3.20-3.05 (br s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2, 160.5, 160.4, 156.4, 156.3, 156.2, 155.5, 155.4, 154.9, 152.2, 151.9, 150.5, 150.4, 150.0, 149.1, 147.7, 144.9, 141.4, 141.1, 139.7, 138.6, 135.1, 135.0, 134.9, 134.8, 134.5, 129.9, 129.8, 129.7, 129.5, 127.0, 125.1, 125.0, 124.9, 123.9, 123.3, 122.7, 119.3, 117.8, 116.9, 116.8, 116.6, 116.3, 115.7, 114.9, 112.0, 107.9, 105.6, 61.0, 56.4, 56.0, 55.8, 41.9, 22.3.

MS (ESI) m/z: 1048 $(M+1)^+$.

Rf: 0.50 (CH_2Cl_2:MeOH, 50:1).

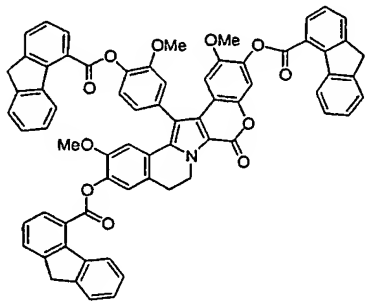
Compound **150**



General procedure **B** (starting from **153**) to afford **150** as a white solid (14 mg, 88%).

^{1}H NMR (300 MHz, CD_3OD) δ 7.47-7.41 (m, 2H), 7.29-7.24 (m, 2H), 7.16 (s, 1H), 6.87 (d, J= 8.2 Hz, 1H), 6.80 (d, J= 10.1 Hz, 1H), 4.42-4.29 (m, 3H), 3.92-3.87 (m, 2H), 3.85 (s, 3H), 3.45 (s, 3H), 3.37 (s, 3H), 3.18 (t, J= 6.2 Hz, 2H), 2.14-1.61 (m, 9H), 1.12-0.98 (m, 18H).
MS (ESI) m/z: 841 $(M+1)^+$.

Compound **151**

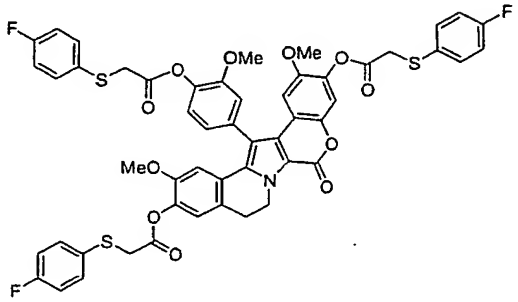


General procedure **D** (starting from **109** and 9H-fluorene-4-carboxylic acid) and chromatography on silica gel (CH_2Cl_2:MeOH, 200:1) to afford **151** as a white solid (26 mg, 48%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56-8.52 (m, 2H), 8.46-8.43 (m, 1H), 8.18-8.11 (m, 3H), 7.77-7.74 (m, 3H), 7.58-7.56 (m, 3H), 7.50-7.30 (m, 13H), 7.21 (s, 1H), 7.04 (s, 1H), 6.93 (s, 1H), 5.04-4.95 (m, 1H), 4.92-4.83 (m, 1H), 3.96 (s, 6H), 3.93 (s, 3H), 3.62 (s, 3H), 3.54 (s, 3H), 3.25 (t, J= 6.5 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 166.0, 166.0, 155.2, 152.6, 150.2, 148.0, 145.2, 145.2, 145.1, 144.2, 144.2, 144.2, 141.5, 141.3, 140.4, 139.9, 139.8, 139.2, 135.2, 134.3, 129.5, 129.3, 129.1, 129.0, 127.7, 127.3, 126.9, 126.8, 126.1, 126.1, 126.0, 125.9, 125.4, 125.1, 125.1, 125.0, 124.7, 124.6, 124.1, 123.4, 122.8, 116.3, 116.1, 115.1, 114.8, 112.2, 109.9, 105.7, 56.3, 55.9, 55.7, 42.6, 37.0 (3C), 28.2.
MS (ESI) m/z: 1100 $(M+23)^+$.
Rf: 0.47 (CH_2Cl_2).

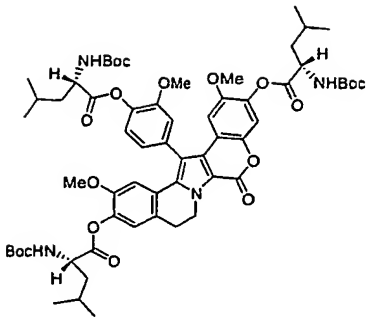
Compound **152**



General procedure **D** (starting from **109** and fluorphenylsulfanylacetic acid) and chromatography on silica gel (hexane:EtOAc, 60:40) to give **152** as a white solid (47 mg, 94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.49 (m, 6H), 7.16-7.00 (m, 10H), 6.86 (s, 1H), 6.74 (s, 1H), 6.64 (s, 1H), 4.89-4.85 (m, 1H), 4.75-4.70 (m, 1H), 3.85 (s, 2H), 3.79 (s, 4H), 3.75 (s, 3H), 3.34 (s, 3H), 3.28 (s, 3H), 3.09 (t, J= 6.6 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 167.5, 167.4, 164.2, 160.9, 154.9, 152.1, 149.7, 147.5, 144.8, 139.7, 139.2, 138.6, 134.9, 134.3, 133.8, 133.7, 133.6, 133.6, 129.3, 129.3, 126.9, 125.9, 125.8, 123.6, 123.1, 122.3, 116.4 (6C), 116.2, 116.1 (6C), 115.8, 115.0, 114.7, 111.7, 109.7, 105.5, 56.1, 55.6, 55.4, 42.4, 37.5 (3C), 27.8.
MS (ESI) m/z: 1006 $(M+1)^+$.
Rf: 0.40 (hexane:EtOAc, 60:40).

Compound **153**



General procedure **D** (starting from **109** and Boc-L-Leu-OH.H_2O) and chromatography on silica gel (hexane:EtOAc, 2:1) to give **153** as a white solid (77 mg, 68%).

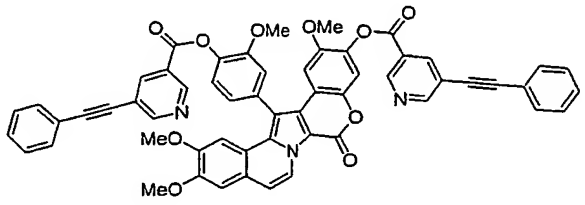
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.08 (m, 4H),6.99 (s, 1H), 6.76 (d, J= 7.0 Hz, 1H), 6.69 (d, J= 8.4 Hz, 1H), 4.94-4.86 (m, 3H), 4.78-4.68 (m, 1H), 4.63-4.50 (m, 2H), 4.37-4.26 (m, 2H), 3.78 (s, 3H), 3.41 (s, 3H), 3.34 (s, 3H), 3.12 (br t, 2H), 1.90-1.60 (m, 9H), 1.45 (s, 27H), 1.05-0.95 (m, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6 (2C), 171.4, 155.6, 155.4, 155.1, 152.1, 149.7, 147.6, 144.8, 139.8, 139.2, 138.7, 135.0, 134.1, 127.0, 127.0, 126.0, 125.7, 123.8, 123.1, 122.5, 116.1, 115.8, 114.9, 114.7, 111.9, 109.7, 105.5, 80.0 (3C), 56.1, 55.7, 55.5, 53.1, 52.2 (2C), 42.4, 41.5 (3C), 28.3 (9C), 28.0, 24.7 (2C), 22.9, 22.8 (4C), 21.8 (2C).

MS (ESI) m/z: 1163 $(M+23)^+$, 1141 $(M+1)^+$.

Rf: 0.26 (hexane:EtOAc, 2:1).

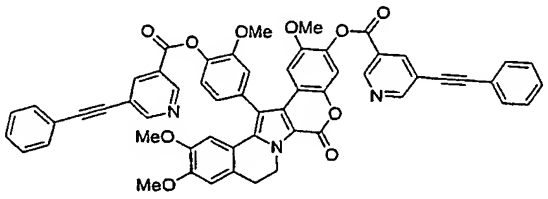
Compound **154**



General procedure **D** (starting from **26** and 5-(2-phenyleth-1-ynyl)nicotinic acid) and chromatography on silica gel (CH_2Cl_2:EtOAc, 4:1) to give **154** as a pale yellow solid (31.0 mg, 88%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.34-9.28 (m, 3H), 9.00-8.97 (m, 2H), 8.63-8.57 (m, 2H), 7.60-7.55 (m, 5H), 7.47-7.31 (m, 9H), 7.28 (s, 1H), 7.15-7.12 (m, 2H), 6.96 (s, 1H), 4.02 (s, 3H), 3.85 (s, 3H), 3.60 (s, 3H), 3.54 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 162.6, 156.0, 154.9, 152.3, 150.4, 149.9, 149.6, 147.6, 145.5, 139.9 (3C), 139.3, 135.1, 134.2, 131.8, 129.2, 129.1, 128.5 (2C), 128.2, 124.7, 124.7, 123.9 (2C), 123.1, 122.0 (2C), 120.8, 118.9, 116.3, 115.5, 113.1, 112.1, 110.9, 108.4, 107.5, 106.3, 105.1, 94.1 (2C), 84.7 (2C), 56.3, 56.0, 55.9, 55.7.
MS (ESI) m/z: 946 $(M+23)^+$, 924 $(M+1)^+$.
Rf: 0.48 (CH_2Cl_2:EtOAc, 4:1).

Compound **155**

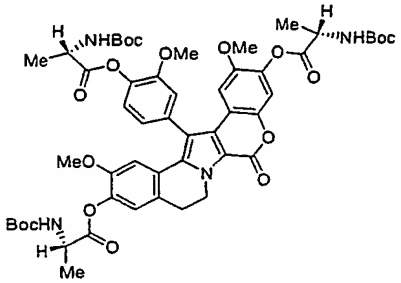


General procedure **D** (starting from **95** and 5-(2-phenyleth-1-ynyl)nicotinic acid) and chromatography on silica gel (CH_2Cl_2:EtOAc, 4:1) to give **155** as a pale yellow solid (37.0 mg, 98%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.32 (br d, J= 1.9 Hz, 1H), 9.28 (br d, J= 1.9 Hz, 1H), 8.99-8.97 (m, 2H), 8.60 (t, J= 1.9 Hz, 1H), 8.6 (t, J= 1.9 Hz, 1H), 7.59-7.55 (m, 4H), 7.40-7.36 (m, 7H), 7.26-7.21 (m, 3H), 6.84 (s, 1H), 6.80 (s, 1H), 6.75 (s, 1H), 4.95-4.75 (m, 2H), 3.92 (s, 3H), 3.82 (s, 3H), 3.51 (s, 3H), 3.50 (s, 3H), 3.16 (t, J= 6.6 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 156.0, 155.0, 152.1, 149.8, 149.2, 147.7, 147.6, 144.9, 139.9, 139.8, 139.6, 138.4, 135.9, 134.8, 131.7, 129.2, 129.1, 128.5, 128.5, 127.4, 126.5, 124.8 (2C), 123.7, 123.5, 122.0 (2C), 120.7, 119.6, 116.5, 115.0, 114.7, 114.5, 111.9, 111.0, 108.5, 105.6, 94.0, 93.9, 84.7 (2C), 56.2, 55.9, 55.8, 55.5, 42.5, 28.6.
MS (ESI) m/z: 926 $(M+1)^+$.
Rf: 0.48 (CH_2Cl_2:EtOAc, 4:1).

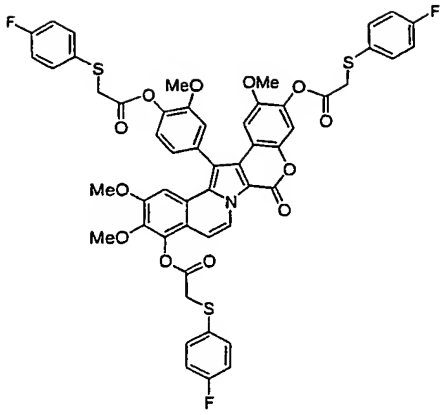
Compound **156**



General procedure **D** (starting from **109** and Boc-L-Ala-OH) and chromatography on silica gel (hexane:EtOAc, from 2:1 to 1:1) to give **156** as a white solid (81 mg, 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.09 (m, 4H), 6.97 (s, 1H), 6.75 (d, J= 7.7 Hz, 1H), 6.67 (d, J= 10.1 Hz, 1H), 5.12 (br s, 2H), 4.89-4.85 (m, 1H), 4.70-4.55 (m, 3H), 3.78 (s, 3H), 3.40 (s, 3H), 3.33 (s, 3H), 2.03 (br t, 2H), 1.58 (d, J= 7.1 Hz, 3H), 1.52 (d, J= 7.1 Hz, 6H), 1.47 (s, 9H), 1.45 (s, 18H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 155.0, 152.0, 149.7, 147.4, 144.8, 139.7, 139.1, 138.6, 135.0, 134.1, 126.9, 126.8, 126.0, 125.9, 125.7, 123.7, 123.1, 122.4, 116.1, 115.8, 114.9, 114.7, 111.7, 109.6, 105.4, 79.9, 60.3, 56.1, 55.7, 55.7, 55.5, 55.4, 49.2, 42.3, 28.2, 27.9, 21.0, 18.5, 14.1.
MS (ESI) m/z: 1037 $(M+23)^+$, 1015 $(M+1)^+$.
Rf: 0.44 (hexane:EtOAc, 1:1).

Compound **157**

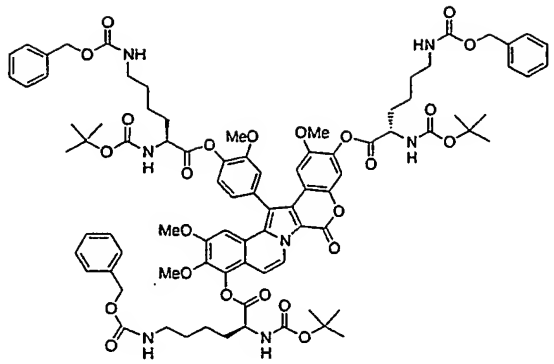


General procedure **E** (starting from **161**, reaction time 24 h) and chromatography on silica gel (hexane:EtOAc, 3:2) to give **157** as a yellow solid (27.1 mg, quant.).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.16 (d, J= 7.8 Hz, 1H), 7.60-7.50 (m, 6H), 7.22-7.20 (m, 1H), 7.10-7.00 (m, 10H), 6.75 (s, 2H), 3.93 (s, 2H), 3.87 (s, 2H), 3.82 (s, 3H), 3.80 (s, 2H), 3.79 (s, 3H), 3.45 (s, 3H), 3.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 167.7, 167.7, 164.6, 164.5, 161.3, 161.2, 155.1, 153.4, 152.5, 147.8, 145.6, 142.1, 140.3, 139.8, 138.9, 134.8, 134.1, 134.0, 133.4, 128.5, 124.0, 123.9, 123.7, 121.2, 118.3, 116.9, 116.6, 116.5, 116.4, 116.1, 115.4, 115.4, 112.3, 112.2, 112.1, 109.2, 106.7, 106.5, 104.5, 61.2, 56.5, 55.9, 55.8, 37.8. MS (APCI) m/z: 1034 $(M+1)^+$.

Rf: 0.63 (hexane:EtOAc, 3:2).

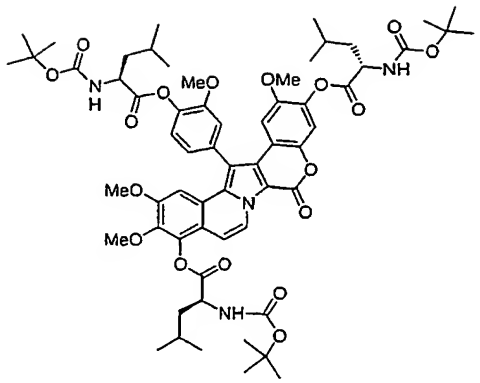
Compound **158**



General procedure **E** (starting from **74**, reaction time 6 d) and chromatography on silica gel (hexane:EtOAc, 2:3) to give **158** as a yellow solid (48.3 mg, 68%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.20 (d, J= 7.5 Hz, 1H), 7.33-7.06 (m, 21H), 6.77 (d, J= 8.4 Hz, 1H), 5.09 (s, 6H), 4.94-4.91 (m, 3H), 4.56 (m, 3H), 3.85 (s, 3H), 3.79 (s, 3H), 3.48 (s, 3H), 3.41 (s, 3H), 3.25-3.24 (m, 6H), 2.19-1.82 (m, 6H), 1.62-1.50 (m, 12H), 1.46-1.45 (m, 27H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 170.9 (2C), 156.8 (3C), 156.0, 155.7, 155.1, 153.3 (2C), 152.5, 147.8, 145.6 (2C), 141.9, 140.2, 139.6 (2C), 139.1 (2C), 136.8, 136.7, 136.2, 134.8, 133.5 (2C), 128.8, 128.3, 124.3, 123.9, 123.7, 121.2, 118.5, 116.1, 115.4, 112.3, 109.2, 107.1, 106.4, 104.6, 80.6, 80.4 (2C), 66.9 (3C), 61.1, 56.5, 56.0 (2C), 54.0, 53.7 (2C), 40.8, 40.7 (2C), 32.3, 32.0 (2C), 29.8 (3C), 28.6 (9C), 22.6, 22.5 (2C).
MS (ESI) m/z: 1638 $(M+23)^+$.
Rf: 0.44 (hexane:EtOAc, 2:3).

Compound **159**



General procedure **E** (starting from **76**, reaction time 6 d) and chromatography on silica gel (hexane:EtOAc, 2:1) to give **159** as a yellow solid (27.9 mg, 69%).

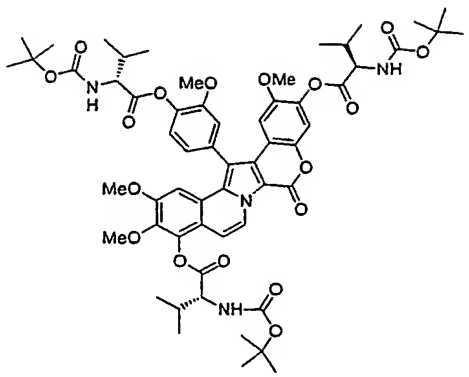
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (d, J= 7.6 Hz, 1H), 7.32-7.08 (m, 6 H), 6.80-6.77 (m, 1H), 5.01-4.98 (m, 3H), 6.60 (m, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.48 (s, 3H), 3.43 (s, 3H), 1.91-1.62 (m, 9H), 1.50-1.46 (m, 27H), 1.06-0.99 (m, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 171.4, 155.6, 155.5, 155.3, 155.0, 153.2, 152.3, 147.6, 145.5, 145.4, 141.7, 140.1, 139.6, 139.0, 134.5, 133.2 (2C), 128.3, 124.0, 123.6, 123.5, 121.0, 118.4, 115.8, 115.1, 112.1, 109.0, 107.0, 106.2, 104.2, 80.4, 80.1 (2C), 56.2, 55.8, 55.7, 55.6, 52.6, 52.2 (2C), 41.7, 41.5, 41.3, 28.3 (9C), 24.8 (3C), 23.0, 22.9 (3C), 21.9, 21.8.

MS (ESI) m/z: 1191 $(M+23)^+$.

Rf: 0.55 (hexane:EtOAc, 2:1).

Compound **160**



General procedure **E** (starting from **75**, reaction time 3 d) and chromatography on silica gel (hexane:EtOAc, 2:1) to give **160** as a yellow solid (37.8 mg, 77%).

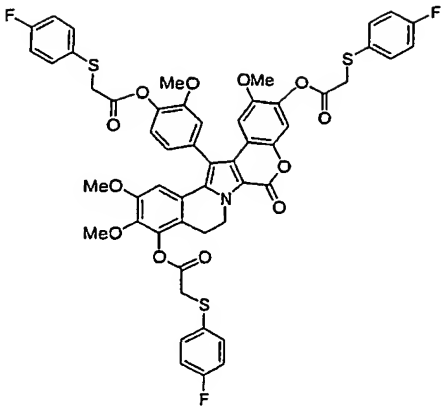
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (d, J= 7.6 Hz, 1H), 7.33-7.09 (m, 6 H), 6.78 (d, J= 8.8 Hz, 1H), 5.12-5.06 (m, 3H), 4.63-4.53 (m, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.49 (s, 3H), 3.43 (s, 3H), 2.46-2.35 (m, 3H), 1.49-1.44 (m, 27H), 1.31-1.01 (m, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4 (3C), 155.9, 155.7, 154.9, 153.1 (2C), 152.2, 147.6, 145.4 (2C), 141.7, 139.9, 138.7, 134.6, 133.2 (2C), 124.0, 123.6, 123.5, 121.0, 118.3, 115.8, 115.1, 112.1 (2C), 109.0, 106.9, 106.1, 104.2, 80.3, 79.9 (2C), 60.7, 59.0, 58.5 (2C), 56.0, 55.7, 55.6, 31.3, 31.1, 30.9, 28.3 (9C), 19.3, 19.2, 19.0, 17.5, 17.2, 17.1.

MS (ESI) m/z: 1149 $(M+23)^+$, 1127 $(M+1)^+$.

Rf: 0.42 (hexane:EtOAc, 2:1).

Compound **161**



General procedure **D** (starting from **1** and 2-[(4-fluorophenyl)thio]acetic acid) and chromatography on silica gel (hexane:EtOAc, 3:2) to give a yellow solid which contained 2-[(4-fluorophenyl)thio]acetic acid. The solid was dissolved in CH_2Cl_2 (20 mL) and washed with NaOH 1 M (20 mL) to give **161** as a pale yellow solid (52.3 mg, 54%).

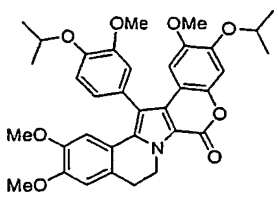
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.49 (m, 6H), 7.16-7.00 (m, 10H), 6.64 (s, 1H), 6.63 (s, 1H), 4.80-4.76 (m, 1H), 4.70-4.55 (m, 1H), 3.87 (s, 2H), 3.85 (s, 2H), 3.79 (s, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 3.35 (s, 3H), 3.34 (s, 3H), 2.90 (br t, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 167.5, 167.4, 164.2, 160.9, 154.8, 152.1, 151.8, 147.5, 144.8, 141.3, 141.1, 139.7, 138.6, 134.7, 134.3, 133.7 (2C), 133.6, 133.5, 133.4, 129.3 (2C), 126.9, 123.5, 123.2, 122.6, 119.0, 116.5, 116.3, 116.2, 116.1, 116.0, 115.6, 114.7, 111.6, 107.6, 105.5, 60.8, 56.2, 55.6, 55.4, 41.8, 37.5, 37.4, 37.3, 29.6.

MS (ESI) m/z: 1057 $(M+23)^+$, 1035 $(M+1)^+$.

Rf: 0.71 (hexane:EtOAc, 1:1).

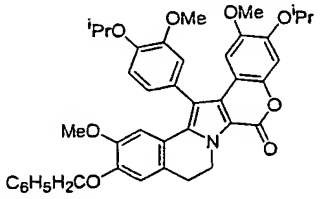
Compound **162**



General procedure **G** (starting from 6,7-Dimethoxy-3,4-dihydroisoquinoline) and chromatography on silica gel (hexane:EtOAc, 2:1) to afford **162** as a pale yellow solid (274.8 mg, 47%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11-7.03 (m, 3H), 6.91 (s, 1H), 6.75 (s, 1H), 6.73 (s, 1H), 6.67 (s, 1H), 4.83-4.61 (m, 2H), 4.59-4.51 (m, 2H), 3.89 (s, 3H), 3.82 (s, 3H), 3.42, 3.36 (s, 3H), 3.12 (t, J= 6.8 Hz, 2H), 1.39-1.36 (m, 12H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 152.0, 148.6, 147.1, 146.6, 146.1, 145.5, 135.5, 128.2, 127.8, 126.3, 123.1, 119.7, 116.6, 114.5, 114.4, 113.3, 110.7, 110.0, 108.3, 104.5, 103.0, 71.4, 71.0, 55.9, 55.6, 55.1, 54.7, 42.0, 28.3, 21.6, 21.5, 21.5, 21.4.
MS (ESI) m/z: 600 $(M+1)^+$.
Rf: 0.17 (hexane:EtOAc, 2:1).

Compound **163**



General procedure **G** (starting from 6-Benzyloxy-7-methoxy-3,4-dihydroisoquinoline) and chromatography on silica gel (hexane:EtOAc, 2:1) to afford **163** as a pale yellow solid (42.5 mg, 34%).

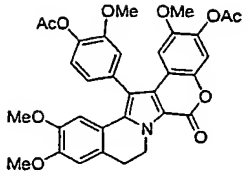
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.29 (m, 5H), 7.09-7.03 (m, 3H), 6.90 (s, 1H), 6.76 (s, 1H), 6.75 (s, 1H), 6.66 (s, 1H), 5.14 (s, 2H), 4.79-4.50 (m, 4H), 3.82 (s, 3H), 3.42 (s, 3H), 3.37 (s, 3H), 3.04 (t, J= 6.8 Hz, 2H), 1.39-1.36 (m, 12H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 151.2, 148.0, 148.0, 147.0, 146.9, 146.5, 145.9, 136.6, 135.8, 128.6, 128.5, 128.2, 128.0, 127.1, 126.4, 125.4, 123.4, 120.5, 116.9, 114.9, 114.5, 113.7, 113.3, 110.3, 109.0,

108.5, 104.8, 103.4, 71.7, 71.4, 70.9, 56.1, 55.4, 55.1, 42.3, 28.6, 21.8 (4C).

MS (ESI) m/z: 676 $(M)^+$.

Rf: 0.30 (hexane:EtOAc, 2:1).

Compound **164**



General procedure **L** (starting from **95**) to afford **164** as a brown solid (7 mg, quant.).

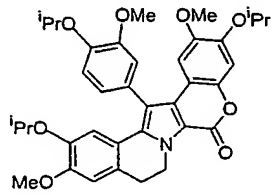
^1H NMR (300 MHz, $CDCl_3$) δ 7.23-7.09 (m, 4H), 6.76 (s, 1H), 6.72 (s, 1H), 6.69 (s, 1H), 4.90-4.74 (m, 2H), 4.30 (t, J= 6.6 Hz, 2H), 3.90 (s, 3H), 3.80 (s, 3H), 3.43 (s, 3H), 3.16 (s, 3H), 3.14 (t, J= 6.6 Hz, 2H), 2.34 (s, 3H), 2.31 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 152.1, 149.1, 147.7 (2C), 139.9, 138.8, 134.3, 130.9, 128.8, 126.4, 126.3, 123.8, 123.3, 119.7, 116.2, 114.8 (2C), 111.9, 111.0, 108.5, 105.5, 56.2, 55.9, 55.7, 55.4, 42.5, 29.7 (2C), 29.4.

MS (ESI) m/z: 600 $(M+1)^+$.

Rf: 0.27 (EtOAc:hexane, 2:1).

Compound **165**



General procedure **G** (starting from 7-Isopropoxy-6-methoxy-3,4-dihydroisoquinoline) and chromatography on silica gel (hexane:EtOAc, 50:50) to afford **165** as a pale yellow solid (84.6 mg, 23%).

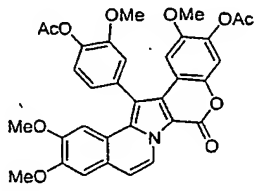
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08-7.00 (m, 3H), 6.86 (s, 1H), 6.74 (s, 2H), 6.60 (s, 1H), 4.78-4.71 (m, 2H), 4.60-4.41 (m, 2H), 3.88-3.77 (m, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.40 (s, 3H), 3.08 (t, J= 6.8 Hz, 2H), 1.40 (d, J= 6.1 Hz, 6H), 1.33 (d, J= 6.0 Hz, 6H), 1.10 (d, J= 6.1 Hz, 3H), 1.07 (d, J= 6.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 151.1, 149.9, 147.0, 146.8, 146.4, 145.8, 145.7, 135.8, 128.3, 128.2, 126.4, 123.2, 119.9, 116.2, 114.7, 114.3, 113.5, 111.9, 111.4, 110.3, 104.8, 103.3, 71.5, 71.3, 70.7, 55.9, 55.8, 55.3, 42.3, 28.6, 21.9, 21.8, 21.7, 21.5(2C), 20.9.

MS (ESI) m/z: 650 $(M+23)^+$, 628 $(M+1)^+$.

Rf: 0.41 (hexane:EtOAc, 50:50).

Compound **166**



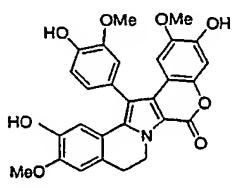
General procedure **L** (starting from **26**) and chromatography on silica gel (CH_2Cl_2:MeOH, 20:1) to afford **166** (7 mg, quant.).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.30 (d, J= 7.6 Hz, 1H), 7.31-7.26 (m, 5H), 7.23-7.10 (m, 2H), 6.84 (s, 1H), 4.00 (s, 3H), 3.83 (s, 3H), 3.51 (s, 3H), 3.46 (s, 3H), 2.37 (s, 2H), 2.32 (s, 2H).

MS (ESI) m/z: 620 $(M+23)^+$, 598 $(M+1)^+$.

Rf: 0.60 (CH_2Cl_2:MeOH, 10:1).

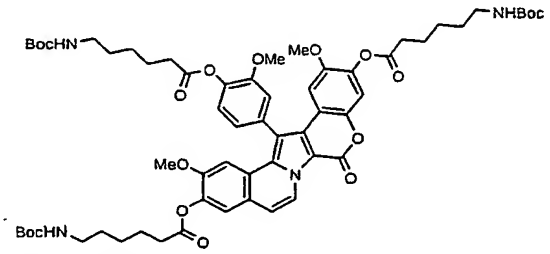
Compound **167**



General procedure **A** (starting from **165**) and chromatography on silica gel (CH_2Cl_2:MeOH, 20:1) to afford **167** as a beige solid (35.3 mg, 55%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.66 (br s, 1H), 9.26 (br s, 1H), 8.85 (br s, 1H), 6.99-6.94 (m, 3H), 6.83 (dd, J= 7.8, 1.7 Hz, 1H), 6.78 (s, 1H), 6.66 (s 1H), 6.46 (s, 1H), 4.62 (br t, J= 5.9 Hz, 2H), 3.79 (s, 3H), 3.73 (s, 3H), 3.33 (s, 3H), 3.06 (br t, J= 5.9 Hz, 2H).
^{13}C NMR (75 MHz, DMSO-d_6) δ 154.3, 148.4, 148.0, 146.8, 146.5, 145.6, 144.8, 144.4, 135.4, 127.9, 125.5, 125.3, 123.3, 119.7, 116.4, 114.8, 114.5, 112.8, 112.4, 111.9, 108.8, 105.0, 103.5, 55.9, 55.6, 55.0, 42.0, 28.0.
MS (ESI) m/z: 524 $(M+23)^+$, 502 $(M+1)^+$.
Rf: 0.25 (CH_2Cl_2:MeOH, 20:1).

Compound **168**



General procedure **D** (starting from **3** and 6-(BOC-amino)caproic acid) and chromatography on silica gel (CH_2Cl_2:MeOH, 40:1) to afford **168** as a white solid (608 mg, 89%).

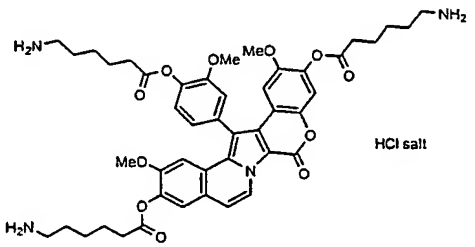
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (d, J= 7.3 Hz, 1H), 7.38 (s, 1H), 7.29-7.13 (m, 5H), 7.07 (d, J= 7.5 Hz, 1H), 6.80 (s, 1H), 4.56 (bs, 3H), 3.82 (s, 3H), 3.44 (s, 6H), 3.20-3.13 (m, 6H), 2.66-2.56 (m, 6H), 1.84-1.75 (m, 6H), 1.60-1.44 (m, 39H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 171.2, 155.9, 155.0, 152.4, 151.0, 147.7, 145.4, 140.9, 140.3, 139.8, 134.1, 133.5, 128.2, 124.0, 123.8, 123.6, 123.5, 123.0, 120.6, 115.5, 115.0, 112.7, 112.2, 112.1, 108.9,

106.3, 106.1, 79.0(3C), 56.2, 55.7, 55.6, 40.3(3C), 33.8(2C), 33.7, 29.7(3C), 28.4(9C), 26.2, 26.1(2C), 24.5(2C), 24.5.

MS (ESI) m/z: 1162 $(M+23)^+$.

Rf: 0.30 (CH_2Cl_2:MeOH, 40:1).

Compound **169**

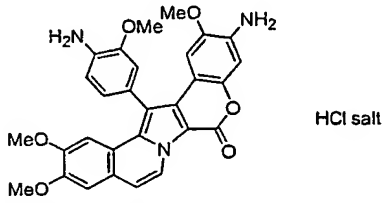


General procedure **C** (starting from **168**) to afford **169** as a white solid (389 mg, 93%).

^1H NMR (300 MHz, CD_3OD) δ 9.07 (d, J= 7.3 Hz, 1H), 7.49 (s, 2H), 7.39 (d, J= 8.1 Hz, 1H), 7.31-7.28 (m, 2H), 7.16-7.11 (m, 2H), 6.86 (s, 1H), 3.88 (s, 3H), 3.46 (s, 6H), 3.02-2.94 (m, 6H), 2.73-2.60 (m, 6H), 1.88-1.75 (m, 12H), 1.54-1.52 (m, 6H).

MS (ESI) m/z: 839 $(M+1)^+$.

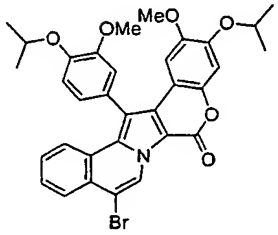
Compound **170**



Me_3SiCl (12 mL, 0.095 mmol) was added to a suspension of **57** (7.0 mg, 0.0136 mmol) in MeOH (2 mL). The solution was stirred at 23 °C for 1 hour. The solvent was evaporated to dryness and CH_2Cl_2 (2 x 1mL) was added in order to remove all the solvent to give **170** as a light orange solid (8 mg, quant.).

^{1}H NMR (300 MHz, CD_3OD) δ 7.70 (d, J= 7.3 Hz, 1H), 7.47 (s, 1H), 7.42 (s, 1H), 7.32 (d, J= 7.3 Hz, 1H), 6.96 (s, 1H), 6.79 (s, 1H), 6.56 (s, 1H),4.90-4.79 (m, 4 H), 3.98 (s, 3H), 3.85 (s, 3H), 3.57 (s 3H), 3.34 (s, 3H).

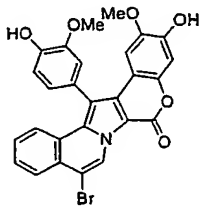
Compound **171**



General procedure **G** (starting from 4-bromoisoquinoline) and chromatography on silica gel (hexane:CH_2Cl_2:Et_2O, 6:4:1) to provide **171** as a yellow solid (41 mg, 16%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (s, 1H), 8.11 (d, J= 7.8 Hz, 1H), 7.76 (d, J= 8.4 Hz, 1H), 7.59 (t, J= 7.7 Hz, 1H), 7.34 (t, J= 7.8 Hz, 1H), 7.17 (d, J= 8.0 Hz, 1H), 7.12-7.05 (m, 2H), 6.96 (s, 1H), 6.64 (s, 1H), 4.70 (hp, J= 6.0 Hz, 1H), 4.57 (hp, J= 6.0 Hz, 1H), 3.83 (s, 3H), 3.44 (s, 3H), 1.51 (d, J= 6.2 Hz, 3H), 1.44 (d, J= 6.0 Hz, 3H), 1.40 (d, J= 7.8 Hz, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 151.5, 148.1, 147.5, 146.7, 146.6, 133.3, 129.8, 128.8, 128.4, 127.6, 127.0, 125.5, 125.0, 124.6, 123.2, 116.6, 114.8, 114.2, 113.5, 109.5, 108.8, 108.4, 105.4, 103.2, 71.5, 56.1, 55.4, 22.3, 21.9, 21.8, 21.7.
Rf: 0.46 (hexane:CH_2Cl_2:Et_2O, 6:4:1).

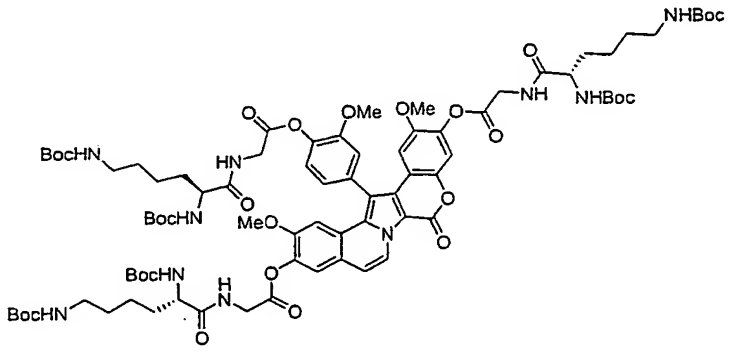
Compound **172**



General procedure **A** (starting from **171**) and chromatography on silica gel (CH_2Cl_2:MeOH from 30:1 to 10:1) to afford **172** as a yellow solid (20 mg, 74%).

^1H NMR (300 MHz, $(CD_3)_2SO$, 40 °C) δ 9.85 (s, 1H), 9.38 (s, 1H), 9.36 (s, 1H), 8.03 (d, J= 8.4 Hz, 1H), 7.79 (d, J= 8.2 Hz, 1H), 7.70 (t, J= 7.3 Hz, 1H), 7.54 (t, J= 7.3 Hz, 1H), 7.20-7.05 (m, 2H), 6.96 (d, J= 7.8 Hz, 1H), 6.87 (s, 1H), 6.55 (s, 1H), 3.74 (s, 3H), 3.37 (s, 3H).
^{13}C NMR (75 MHz, $(CD_3)_2SO$, 60 °C) δ 154.1, 148.8, 148.1, 147.1, 146.2, 144.7, 132.2, 129.4, 129.1, 128.6, 127.2, 126.2, 124.4, 123.9, 123.0, 116.7, 114.5, 113.5, 107.7, 107.3, 105.8, 103.6, 72.0, 55.9, 55.0. MS (APCI) m/z: 534 $(M+2)^+$, 532 $(M)^+$.
Rf: 0.50 (CH_2Cl_2:MeOH, 20:1).

Compound **173**

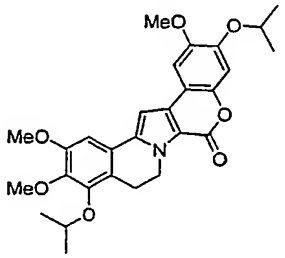


General procedure **D** (starting from **3** and Boc-Lys(Boc)Gly-OH) and chromatography on silica gel (CH_2Cl_2:MeOH, 30:1) to afford **173** as a pale yellow solid (98 mg, 74%).

^1H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, J= 7.3 Hz, 1H), 7.70-7.40 (m, 3H), 7.30-7.00 (m, 6H), 6.80-6.60 (m, 2H), 6.40 (d, J= 7.1 Hz, 1H), 5.67 (br s, 2H), 5.41 (br s, 1H), 4.91 (br s, 1H), 4.82 (br s, 2H), 4.50-4.20 (m, 9H), 3.90 (s, 3H), 3.42 (s, 6H), 3.05 (br s, 6H), 1.90-1.60 (m, 6H), 1.50-1.30 (m, 66H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 172.8, 167.8, 167.7, 156.3, 156.1, 155.9, 154.1, 152.1, 150.6, 147.5, 144.7, 140.0, 139.6, 138.9, 134.4, 132.9, 127.4, 123.7, 123.4, 123.3, 121.9, 121.0, 115.4, 112.2, 111.9, 108.2, 106.0, 105.7, 79.9, 78.9, 56.4, 55.7, 55.5, 54.3, 53.4, 40.9, 39.8, 31.9, 29.6, 28.4, 28.3, 28.2, 27.7, 22.5. MS (APCI) m/z: 1678 $(M+23)^+$.
Rf: 0.21 (CH_2Cl_2:MeOH, 30:1).

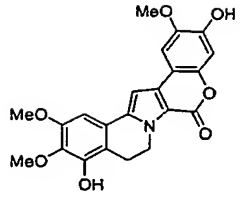
Compound **174**



General procedure **H** (starting from 6,7-dimethoxy-5-isopropoxy-3,4-dihydroisoquinoline) and chromatography on silica gel Merck Si60 (230-400 mesh) (CH_2Cl_2:MeOH, 100:1) to afford **174** as a clear oil (150 mg, 43%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (s, 1H), 7.00 (s, 1H), 6.92 (s, 1H), 6.81 (s, 1H), 4.70-4.50 (m, 4H), 3.95 (s, 6H), 3.88 (s, 3H), 3.10 (t, J= 6.7 Hz, 2H), 1.41 (d, J= 6.2 Hz, 6H), 1.31 (d, J= 6.2 Hz, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 152.7, 148.9, 147.6, 147.2, 145.9, 143.2, 139.7, 130.9, 122.8, 120.4, 115.1, 109.9, 104.6, 103.6, 103.4, 96.0, 75.6, 71.5, 60.6, 56.4, 56.1, 42.0, 22.6, 22.5, 21.8.
MS (ESI) m/z: 494 $(M+1)^+$.
Rf: 0.40 (CH_2Cl_2:MeOH, 100:1).

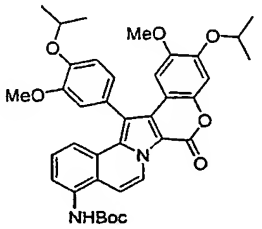
Compound **175**



Gerenal procedure **A** (starting from **174**) and chromatography on silica gel Merck Si60 (230-400 mesh) (CH_2Cl_2:MeOH, 50:1) to afford **175** as a brown solid (15 mg, 62%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (s, 1H), 6.99 (s, 1H), 6.84 (s, 1H), 6.81 (s, 1H), 5.99 (s, 1H), 5.84 (s, 1H), 4.70 (t, *J*= 6.9 Hz, 2H), 4.01 (s, 3H), 3.96 (s, 6H), 3.11 (t, J= 6.9 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 151.3, 146.6, 146.4, 146.0, 143.9, 139.6, 136.1, 130.9, 123.1, 115.3, 112.4, 109.9, 103.7, 103.4, 100.1, 96.0, 61.2, 56.4, 56.0, 41.9, 21.3.
MS (ESI) m/z: 410 $(M+1)^+$.
Rf: 0.44 (CH_2Cl_2:MeOH, 20:1).

Compound **176**

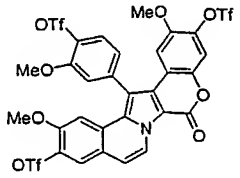


Gerenal procedure **H** (starting from 5-Boc-aminoisoquinoline) and chromatography on silica gel Merck Si60 (230-400 mesh) (CH_2Cl_2:MeOH:Et_3N, 100:1:0.5) to afford **176** as a brown solid (120 mg, 10%).

^1H NMR (300 MHz, $CDCl_3$) δ 9.61 (s, 1H), 8.11 (d, *J*= 7.8 Hz, 1H), 7.76 (d, *J*= 8.4 Hz, 1H), 7.59 (t, *J*= 7.7 Hz, 1H), 7.34 (t, *J*= 7.8 Hz, 1H), 7.17 (d, *J*= 8.0 Hz, 1H), 7.12-7.05 (m, 2H), 6.96 (s, 1H), 6.64 (s, 1H), 4.70

(hp, J= 6.0 Hz, 1H), 4.57 (hp, J= 6.0 Hz, 1H), 3.83 (s, 3H), 3.44 (s, 3H), 1.51 (d, J= 6.2 Hz, 3H), 1.44 (d, J= 6.0 Hz, 3H), 1.40 (d, J= 7.8 Hz, 6H).
MS (ESI) m/z: 653 $(M+1)^+$.
Rf: 0.33 (CH_2Cl_2:MeOH, 100:1).

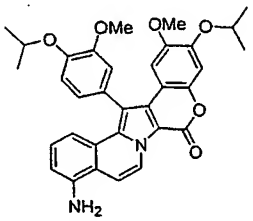
Compound **177**



General procedure **I** (starting from **3**) and chromatography on silica gel (CH_2Cl_2) and triturated with Et_2O (50 mL) to afford **177** as a white solid (434.7 mg, 82%).

^1H NMR (300 MHz, $CDCl_3$) δ 9.31 (d, J= 7.3 Hz, 1H), 7.62 (s, 1H), 7.57 (d, J= 8.5 Hz, 1H), 7.35-7.32 (m, 3H), 7.16 (d, J= 7.6 Hz, 1H), 7.14 (s, 1H), 6.74 (s, 1H), 3.97 (s, 3H), 3.50 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 152.9, 150.9, 148.1, 145.0, 139.4, 139.0, 138.1, 136.7, 132.7, 127.3, 124.9, 124.0, 123.8, 123.7, 121.0, 120.8, 117.5, 116.5, 115.8, 113.2, 112.3, 109.9, 106.8, 106.4, 56.8, 55.9, 55.7.
MS (ESI) m/z: 896 $(M+1)^+$.
Rf: 0.32 (hexane:EtOAc, 6:1).

Compound **178**

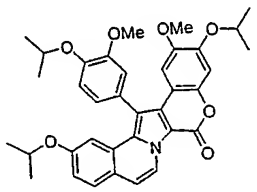


$AlCl_3$ (12 mg, 0.092 mmol) was added to a solution of **176** (20 mg, 0.030 mmol) in anhydrous CH_2Cl_2 (2 mL) under Argon atmosphere. The reaction mixture was stirred for 2.5 hours at 23 °C. The mixture was

quenched with H_2O (10 mL, pH=4-5), extracted with CH_2Cl_2 (3x10 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulted residue was subjected to flash chromatography on silica gel Merck Si60 (230-400 mesh) (CH_2Cl_2:MeOH, 30:1) to provide **178** as a white solid (7 mg, 42%).

^1H NMR (300 MHz, $CDCl_3$) δ 9.28 (d, J= 7.7 Hz, 1H), 7.25-7.05 (m, 6H), 6.97 (s, 1H), 6.82 (d, J= 7.7 Hz, 1H), 6.65 (s, 1H), 4.69 (hp, J= 6.2 Hz, 1H), 4.57 (hp, J= 6.2 Hz, 1H), 4.12 (bs, 2H), 3.82 (s, 3H), 3.43 (s, 3H), 1.49 (d, J= 5.9 Hz, 3H), 1.43 (d, J= 5.9 Hz, 3H), 1.40 (d, J= 6.2 Hz, 6H).
MS (ESI) m/z: 553 $(M+1)^+$.
Rf: 0.55 (CH_2Cl_2:MeOH, 30:1).

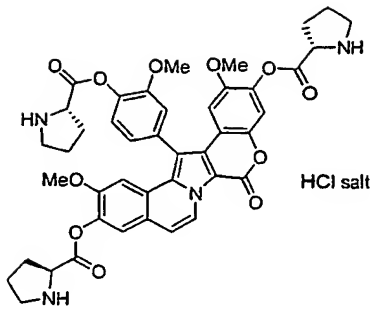
Compound **179**



General procedure **H** (starting from 7-isopropylisoquinoline) and chromatography on reverse silica gel RP-18 (CH_3CN:H_2O, 4:1 then CH_3CN) to afford **179** as a yellow oil (6 mg, 2%).

^1H NMR (300 MHz, $CDCl_3$) δ 9.20 (d, J= 7.3 Hz, 1H), 7.61 (d, J= 7.3 Hz, 1H),7.17-7.05 (m, 6H), 6.98 (s, 1H), 6.70 (s, 1H), 4.65-4.58 (m, 2H), 4.1-3.95 (m, 1H), 3.83 (s, 3H), 3.44 (s, 3H), 1.47 (d, J= 6.1 Hz, 6H), 1.40 (d, J= 6.1 Hz, 6H), 1.17-1.12 (m, 6H).
MS (ESI) m/z: 596 $(M+1)^+$.
Rf: 0.31 (CH_3CN, RP-18).

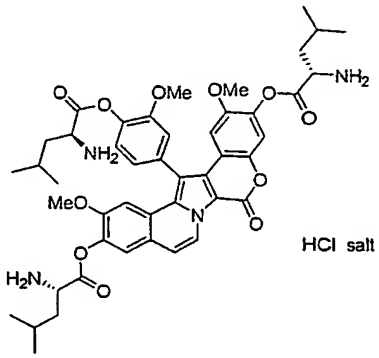
Compound **180**



General procedure **C** (starting from **127**) to afford **180** as a pale yellow solid (156 mg, 88%).

^{1}H NMR (300 MHz, CD_3OD) δ 9.17 (dd, J= 7.6, 2.6 Hz, 1H), 7.69 (d, J= 2.7 Hz, 1H), 7.65-7.55 (m, 2H), 7.50-7.20 (m, 4H), 6.90 (d, J= 10.6 Hz, 1H), 4.80-4.60 (m, 3H), 3.92 (s, 3H), 3.91 (s, 3H), 3.60-3.40 (m, 12H), 2.70-2.30 (m, 6H), 2.30-10 (m, 6H).
MS (ESI) m/z: 791 $(M+1)^+$.

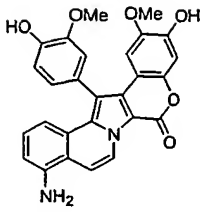
Compound **181**



General procedure **C** (starting from **146**) to afford **181** as a white solid (390 mg, 84%).

^{1}H NMR (300 MHz, CD_3OD) δ 9.26 (d, J= 7.5 Hz, 1H), 7.69 (s, 1H), 7.60-7.50 (m, 2H), 7.45-7.30 (m, 4H), 6.92 (d, J= 6.6 Hz, 1H), 4.50-4.30 (m, 3H), 3.88 (s, 3H), 3.48 (s, 6H), 2.20-1.70 (m, 6H), 1.20-1.00 (m, 18H).
MS (ESI) m/z: 840 $(M+1)^+$.

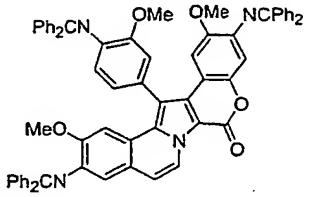
Compound **182**



General procedure **A** (starting from **178**) and chromatography on silica gel Merck Si60 (230-400 mesh) (CH_2Cl_2:MeOH, 30:1) to afford **182** as a white solid (3.8 mg, 76%).

^1H NMR (300 MHz, CD_3OD) δ 9.15 (d, J= 7.7 Hz, 1H), 7.20-7.15 (m, 2H), 7.10-6.95 (m, 4H), 6.89 (s, 1H), 6.82 (d, J= 7.7 Hz, 1H), 6.57 (s, 1H), 3.81 (s, 3H), 3.44 (s, 3H).
MS (ESI) m/z: 469 $(M+1)^+$.
Rf: 0.12 (CH_2Cl_2:MeOH, 40:1).

Compound **183**



A suspension of **177** (0.33 g, 0.37 mmol), $Pd(OAc)_2$ (12.5 mg, 0.055 mmol), BINAP (69.2 mg, 0.111 mmol) in anhydrous toluene (5 mL) was stirred at 23 °C under Argon atmosphere for 5 min. Then benzophenone imine (218 mL, 1.30 mmol) was added and the mixture was stirred at 110 °C for 7 days. The reaction was cool down to 23 °C, H_2O (20 mL) was added, was extracted with CH_2Cl_2 (3x20 mL), dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was purified by chromatography on silica gel (hexane:EtOAc, 2:1) to give **183** (29.0 mg, 8%) as a yellow solid.

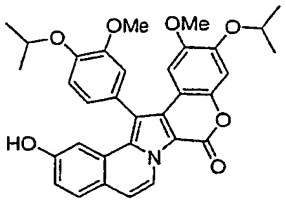
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.11 (d, J=7.5 Hz, 1H), 7.78-7.70 (m, 4H), 7.48-7.13 (m, 26H), 7.07-6.97 (m, 3H), 6.86-6.80 (m, 3H), 6.67 (s, 1H), 6.64 (s, 1H), 3.69 (s, 3H), 3.28 (s, 3H), 3.26 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 169.3, 155.5, 150.3, 150.0, 146.4, 146.0, 142.8, 141.9, 140.9, 139.4, 139.0, 137.0, 136.4, 134.2, 131.1, 130.9, 129.6, 129.4, 128.8, 128.6, 128.5, 128.2, 127.9, 127.9 (4C), 124.1, 123.8, 122.7, 121.7, 121.1, 117.5, 114.4, 113.1, 112.6, 111.9, 109.2, 105.4, 105.2, 55.7, 55.6, 55.3.

MS (ESI) m/z: 989 $(M+1)^+$.

Rf: 0.50 (Hex:EtOAc, 2:1).

Compound **184**



General procedure **G** (starting from 7-hydroxy-isoquinoline) and chromatography on silica gel (CH_2Cl_2:EtOAc, 200:1) to afford **184** as a white solid (112.5 mg, 9%).

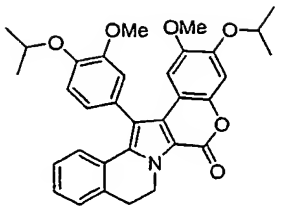
^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 10.0 (br s, 1H), 8.84 (d, J= 7.0 Hz, 1H), 7.61 (d, J= 8.8 Hz, 1H), 7.09-7.01 (m, 3H), 6.71 (s, 2H), 6.6 (s, 1H), 6.5 (s, 1H), 4.64 (m, 1H), 4.42 (m, 1H), 3.33 (s, 3H), 3.31 (s, 3H), 1.27 (d, J= 5.7Hz, 6H), 1.13 (d, J=5.7Hz, 6H).

^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 158.9, 157.0, 155.4, 149.2, 147.6, 147.2, 147.1, 145.7, 133.8, 128.6, 124.5, 121.5, 121.3, 118.6, 114.6, 114.5, 113.9, 110.8, 110.0, 108.3, 106.9, 101.5, 92.8, 83.8, 70.5, 70.1, 55.9, 54.9, 54.8, 21.7 (2C).

MS (ESI) m/z: 575 $(M+1)^+$.

Rf: 0.23 (CH_2Cl_2:EtOAc, 200:1).

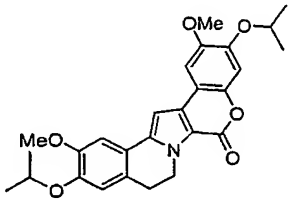
Compound **185**



General procedure **H** (starting from 3,4-dihydroisoquinoline) and chromatography on silica gel (CH_2Cl_2 and then hexane:EtOAc, 2:1) to afford **185** as a pale yellow solid (243 mg, 21%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.28-7.00 (m, 7H), 6.91 (s, 1H), 6.63 (s, 1H), 4.80-4.78 (m, 2H), 4.64 (sep, J= 6.0 Hz, 1H), 4.53 (sep, J= 6.0 Hz, 1H), 3.81 (s, 3H), 3.42 (s, 3H), 317 (t, J= 6.5 Hz, 2H), 1.39-1.37 (m, 12H).
MS (ESI) m/z: 541 $(M+1)^+$.
Rf: 0.50 (hexane:EtOAc, 2:1).

Compound **186**



General procedure **H** (starting from 6-isopropoxy-7-methoxy-3,4-dihydroisoquinoline) and chromatography on silica gel Merck Si60 (230-400 mesh) (CH_2Cl_2:MeOH, from 100:1 to 20:1) to afford **186** as a brown solid (861 mg, 29%).

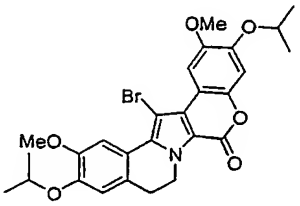
^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (s, 1H), 7.15 (s, 1H), 6.90 (s, 1H), 6.78 (s, 1H), 6.77 (s, 1H), 4.68 (t, J= 6.7 Hz, 2H), 4.62-4.50 (m, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 3.06 (t, J= 6.7 Hz, 2H), 1.40 (d, J= 6.0 Hz, 12H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 149.6, 148.1, 147.6, 147.2, 145.9, 140.1, 131.1, 125.6, 120.0, 115.0, 114.9, 110.0, 108.1, 104.6, 103.6, 95.3, 71.5, 56.4, 56.2, 42.2, 28.2, 22.0, 21.8.

MS (ESI) m/z: 464 $(M+1)^+$.

Rf: 0.44 (hexane:AcOEt, 1:1).

Compound **187**



N-Bromosuccinimide (21 mg, 0.12 mmol) was added in one portion to a solution of **186** (50 mg, 0.10 mmol) in AcOEt (1 mL) under Argon atmosphere. The solution was stirred at 23 °C for 15 minutes, then diluted with AcOEt, quenched with H_2O and washed succesively with HCl 0.1N (2x10 mL) and NaOH 0.1N (2x10 mL).

After drying over Na_2SO_4, the solvent was evaporated under vacuum to afford **187** as a brown solid (56 mg, 96%).

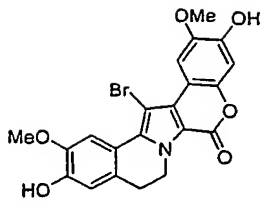
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.12 (s, 1H), 6.89 (s, 1H), 6.81 (s, 1H), 4.73 (t, J= 6.2 Hz, 2H), 4.65-4.50 (m, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 3.02 (t, J= 6.5 Hz, 2H), 1.41 (d, J= 6.0 Hz, 6H), 1.40 (d, J= 6.0 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 148.8, 148.0, 147.6, 146.5, 145.9, 135.2, 127.3, 127.0, 119.2, 114.6, 114.0, 109.6, 109.5, 104.7, 103.2, 86.5, 71.4, 56.3, 56.2, 42.5, 28.8, 22.0, 21.8.

MS (ESI) m/z: 564 $(M+23)^+$.

Rf: 0.58 (hexane:AcOEt, 1:1).

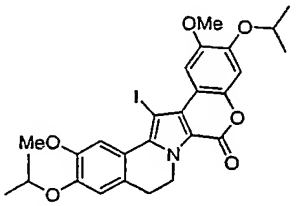
Compound **188**



General procedure **A** (starting from **187**) and chromatography on silica gel Merck Si60 (230-400 mesh) (CH_2Cl_2:MeOH, from 100:1 to 40:1) to afford **188** as a brown solid (15 mg, 40%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1H), 8.11 (s, 1H), 6.87 (s, 1H), 6.79 (s, 1H), 4.67 (t, J= 6.6 Hz, 2H), 3.96 (s, 3H), 3.94 (s, 3H), 2.97 (t, J= 6.6 Hz, 2H).
MS (ESI) m/z: 458 $(M+1)^+$.
Rf: 0.14 (CH_2Cl_2:MeOH, 50:1).

Compound **189**



N-Iodosuccinimide (77 mg, 0.32 mmol) was added in one portion to a solution of **186** (100 mg, 0.21 mmol) in CH_2Cl_2 (4 mL) under Argon atmosphere. The solution was stirred at 23 °C for 30 minutes, then diluted with AcOEt, quenched with H_2O and washed succesively with NaOH 0.1N (2x10 mL) and H_2O (2x10 mL).

After drying over Na_2SO_4, the solvent was evaporated under vacuum to afford **189** as a brown solid (120 mg, 95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.25 (s, 1H), 6.87 (s, 1H), 6.81 (s, 1H), 4.74 (t, J= 6.2 Hz, 2H), 4.65-4.50 (m, 2H), 3.97 (s, 3H), 3.94 (s,

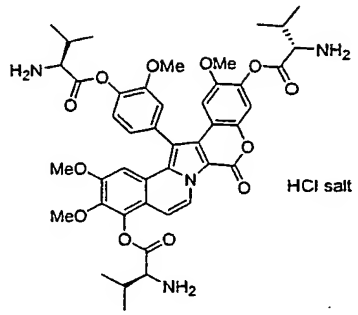
3H), 2.99 (t, *J*= 6.4 Hz, 2H), 1.41 (d, *J*= 6.0 Hz, 6H), 1.40 (d, *J*= 6.0 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 148.4, 148.0, 147.5, 145.9, 137.5, 129.4, 127.7, 119.5, 115.7, 114.6, 110.0, 103.7, 103.2, 71.3, 56.3, 42.5, 29.0, 22.0, 21.8.

MS (ESI) m/z: 590 $(M+1)^+$.

Rf: 0.49 (hexane:AcOEt, 1:1).

Compound **190**

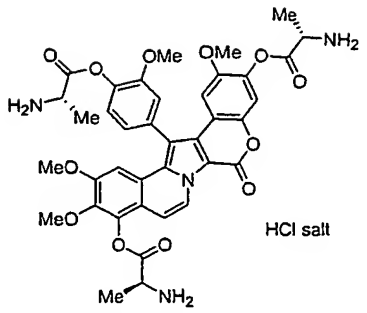


General procedure **C** (starting from **129**) to afford **190** as a white solid (197 mg, 80%).

^{1}H NMR (300 MHz, CD_3OD) δ 9.23 (d, *J*= 7.5 Hz, 1H), 7.60-7.50 (m, 2H), 7.45-7.30 (m, 3H), 7.24 (d, *J*= 7.4 Hz, 1H), 6.92 (d, J= 10.4 Hz, 1H), 4.60 (d, *J*= 3.7 Hz, 1H), 4.36 (d, *J*= 4.3 Hz, 1H), 4.27 (d, *J*= 4.3 Hz, 1H), 3.90 (d, *J*= 1.2 Hz, 3H), 3.89 (d, *J*= 2.4 Hz, 3H), 3.54 (d, *J*= 3.8 Hz, 3H), 3.48 (d, *J*= 3.5 Hz, 3H), 2.70-2.40 (m, 3H), 1.35-1.15 (m, 18H).

MS (ESI) m/z: 827 $(M+1)^+$.

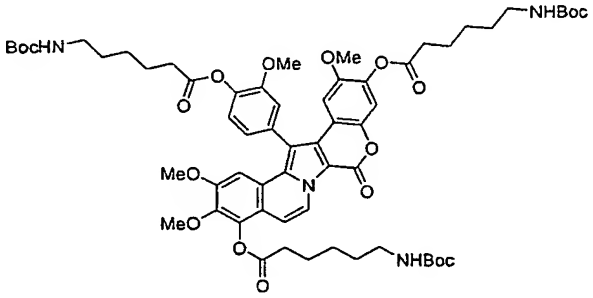
Compound **191**



General procedure **C** (starting from **97**) to afford **191** as a white solid (1.15 g, 94%).

^{1}H NMR (300 MHz, CD_3OD) δ 9.16 (d, *J*= 7.7 Hz, 1H), 7.60-7.50 (m, 2H), 7.40-7.25 (m, 3H), 7.22 (d, J= 7.4 Hz, 1H), 6.88 (d, *J*= 9.1 Hz, 1H), 4.70-4.60 (m, 1H), 4.60-4.50 (m, 1H), 4.50-4.35 (m, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.54 (d, *J*= 2.1 Hz, 3H), 3.48 (d, *J*= 2.1 Hz, 3H), 1.90-1.70 (m, 9H). MS (ESI) m/z: 743 $(M+1)^+$.

Compound **192**



General procedure **D** (starting from **2** and 6-(BOC-amino)caproic acid) and chromatography on silica gel (hexane:EtOAc, 50:50) to afford **192** as a white solid (2.02 g, 92%).

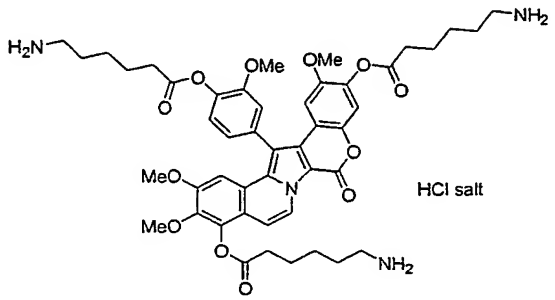
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (d, *J*= 7.5 Hz, 1H), 7.30-7.20 (m, 3H), 7.09 (s, 1H), 7.08 (s, 1H), 7.02 (d, *J*= 7.5 Hz, 1H), 6.78 (s, 1H), 4.61 (bs, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.48 (s, 3H), 3.43 (s, 3H), 3.20-3.10 (m, 6H), 2.74 (t, *J*= 7.3 Hz, 2H), 2.63 (t, *J*= 7.3 Hz, 2H), 2.56 (t, *J*= 7.3 Hz, 2H), 1.90-1.70 (m, 6H), 1.60-1.40 (m, 39H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 171.3, 171.2, 155.9, 154.9, 153.2, 152.4, 147.7, 145.4, 141.7, 140.3, 139.8, 139.0, 134.1, 133.2, 128.3, 124.0, 123.5, 123.3, 120.9, 118.2, 115.5, 115.0, 112.1, 108.8, 106.5, 106.1, 104.0, 79.0, 60.7, 56.2, 55.7, 55.6, 40.3, 33.8, 33.7, 29.7, 28.4, 26.2, 26.0, 24.7, 24.5, 24.4.

MS (ESI) m/z: 1191 $(M+23)^+$.

Rf: 0.19 (hexane:AcOEt, 1:1).

Compound **193**

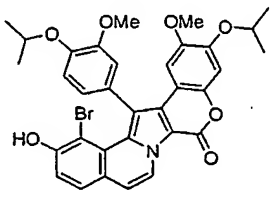


General procedure **C** (starting from **192**) to afford **193** as a white solid (1.45 g, 90%).

^1H NMR (300 MHz, CD_3OD) δ 9.08 (d, J= 8.5 Hz, 1H), 7.44 (d, J= 1.7 Hz, 1H), 7.39 (d, J= 8.0 Hz, 1H), 7.26 (dd, J= 8.1, 1.7 Hz, 1H), 7.20-7.10 (m, 3H), 6.85 (s, 1H), 3.86 (s, 3H), 3.84 (s, 6H), 3.50 (s, 3H), 3.44 (s, 3H), 3.05-2.90 (m, 6H), 2.83 (t, J= 7.3 Hz, 2H), 2.71 (t, J= 7.3 Hz, 2H), 2.61 (t, J= 7.3 Hz, 2H), 1.90-1.50 (m, 18H).

MS (ESI) m/z: 869 $(M+1)^+$.

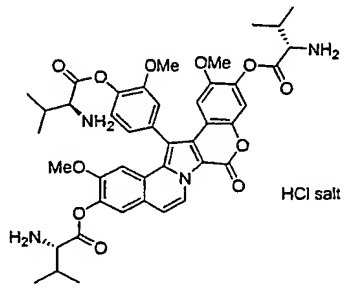
Compound **194**



General procedure **G** (starting from 7-Hydroxy-8-bromo-isoquinoline) and chromatography on silica gel (CH_2Cl_2:EtOAc, 10:1) to afford **194** as a pale yellow solid (9 mg, 2%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.21 (d, J= 6.7 Hz, 1H), 7.63 (d, J= 6.7 Hz, 1H), 7.18-7.05 (m, 5H), 6.96 (s, 1H), 6.62 (s, 1H), 4.72-4.55 (m, 2H), 3.84 (s, 3H), 3.44 (s, 3H), 1.5-1.40 (m, 12H).
Rf: 0.51 (CH_2Cl_2:EtOAc, 10:1).

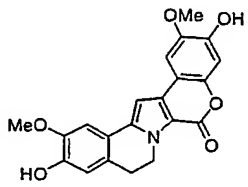
Compound **195**



General procedure **C** (starting from **38**) to afford **195** as a pale yellow solid (654 mg, 83%).

^{1}H NMR (300 MHz, CD_3OD) δ 9.20-9.15 (m, 1H), 7.67 (s, 1H), 7.65-7.55 (m, 2H), 7.50-7.20 (m, 4H), 6.91 (d, J= 8.4 Hz, 1H), 4.40-4.25 (m, 3H), 3.91 (d, J= 3.8 Hz, 3H), 3.49 (s, 6H), 2.70-2.40 (m, 3H), 1.40-1.20 (m, 18H).
MS (ESI) m/z: 797 $(M+1)^+$.

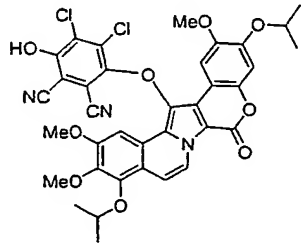
Compound **196**



General procedure **A** (starting from **186**) and chromatography on silica gel Merck Si60 (230-400 mesh) (CH_2Cl_2:MeOH, 40:1) to afford **196** as a brown solid (25 mg, 62%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (s, 2H), 7.00 (s, 1H), 6.86 (s, 1H), 6.76 (s, 1H), 5.83 (bs, 1H), 5.78 (bs, 1H), 4.70 (t, J= 6.4 Hz, 2H), 4.01 (s, 3H), 3.99 (s, 3H), 3.07 (t, J= 6.7 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 147.9, 147.6, 146.6, 145.9, 141.7, 132.7, 132.6, 126.9, 119.4, 115.5, 114.7, 110.1, 108.3, 104.8, 104.2, 95.6, 56.6, 56.4, 42.7, 28.4.
MS (ESI) m/z: 380 $(M+1)^+$.
Rf: 0.22 (CH_2Cl_2:MeOH, 40:1).

Compound **197**

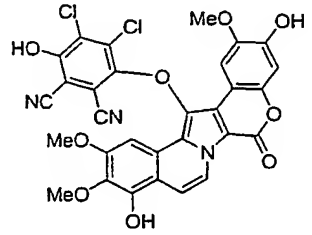


General procedure **E** (starting from **186** and 16 h of reaction time) and chromatography on silica gel Merck Si60 (230-400 mesh) (CH_2Cl_2:MeOH from 50:1 to 10:1) to afford **197** as a beige solid (52 mg, 66 %).

^1H NMR (300 MHz, CD_3OD) δ 8.77 (d, J= 7.7 Hz, 1H), 7.28 (d, J= 7.3 Hz, 1H), 7.20 (s, 1H), 6.81 (s, 1H), 6.63 (s, 1H), 4.75-4.55 (m, 2H), 3.96 (s, 3H), 3.70 (s, 3H), 3.49 (s, 3H), 1.50-1.40 (m, 6H), 1.35-1.25 (m, 6H).
^{13}C NMR (75 MHz, CD_3OD+$CDCl_3$) δ 155.3, 154.0, 151.7, 148.3, 147.0, 146.4, 146.2, 143.7, 142.9, 133.1, 129.3, 129.2, 129.0, 126.8, 122.9,

121.8, 120.4, 119.3, 116.3, 114.0, 111.4, 108.3, 107.1, 104.9, 104.6, 103.1, 100.0, 99.7, 97.9, 76.4, 71.5, 60.5, 55.4, 22.4, 21.5, 21.3.
MS (ESI) m/z: 740 $(M+23)^+$, 718 $(M+1)^+$.
Rf: 0.14 (CH_2Cl_2:MeOH, 10:1).

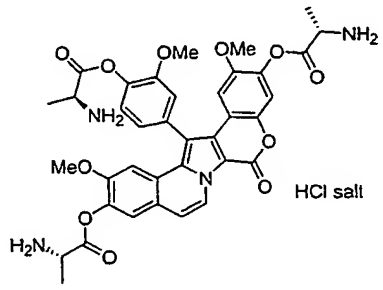
Compound **198**



General procedure **A** (starting from **197**) and chromatography on silica gel Merck Si60 (230-400 mesh) (CH_2Cl_2:MeOH, 5:1) to afford **198** as a brown solid (15 mg, 42%).

^1H NMR (300 MHz, CD_3OD) δ 8.81 (d, J= 7.5 Hz, 1H), 7.31 (d, J= 7.5 Hz, 1H), 6.98 (s, 1H), 6.72 (s, 1H), 6.70 (s, 1H), 3.88 (s, 3H), 3.69 (s, 3H), 3.60 (s, 3H).
MS (ESI) m/z: 634 $(M+1)^+$.
Rf: 0.22 (CH_2Cl_2:MeOH, 5:1).

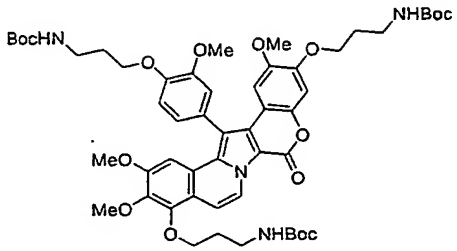
Compound **199**



General procedure **C** (starting from **41**) to afford **199** as a pale yellow solid (537 mg, 80%).

^{1}H NMR (300 MHz, CD_3OD) δ 9.18 (d, J= 7.5 Hz, 1H), 7.67 (s, 1H), 7.60-7.50 (m, 2H), 7.45-7.35 (m, 1H), 7.35-7.25 (m, 3H), 6.91 (d, J= 8.0 Hz, 1H), 4.60-4.40 (m, 3H), 3.90 (d, J= 2.5 Hz, 3H), 3.49 (s, 3H), 3.48 (s, 3H), 1.85-1.60 (m, 9H).
MS (ESI) m/z: 713 $(M+1)^+$.

Compound **200**

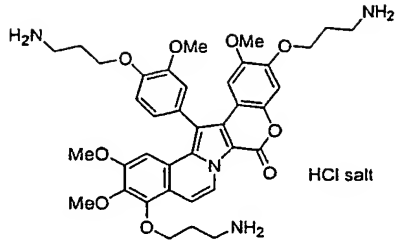


A suspension of **2** (100 mg, 0.18 mmol), Cs_2CO_3 (246 mg, 0.75 mmol) in anhydrous DMF (2 mL) was stirred at 23 °C under Argon atmosphere for 10 minutes, then 3-(BOC-amino)propyl bromide (180 mg, 0.75 mmol) was added and the mixture was heated at 50 °C overnight. The resulting solution was cooled to 23 °C, quenched with H_2O, diluted with EtOAc (50 mL) and washed with H_2O (2x20 mL).

The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the solvent removed under vaccum. The residue was purified by chromatography on silica gel (CH_2Cl_2:MeOH, 30:1) to afford **200** as a white solid (180 mg, 95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.21 (d, J= 7.7 Hz, 1H), 7.36 (d, J= 7.7 Hz, 1H), 7.20-7.10 (m, 3H), 6.97 (s, 1H), 6.93 (s, 1H), 6.70 (s, 1H), 5.50-5.40 (m, 2H), 4.97 (bs, 1H), 4.18 (t, J= 6.4 Hz, 4H), 4.12 (t, J= 5.8 Hz, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.47 (s, 3H), 3.44 (s, 3H), 3.44-3.10 (m, 6H), 2.15-2.00 (m, 6H), 1.48 (s, 9H), 1.45 (s, 9H), 1.44 (s, 9H).
MS (ESI) m/z: 1023 $(M+1)^+$.
Rf: 0.15 (hexane:AcOEt, 1:1).

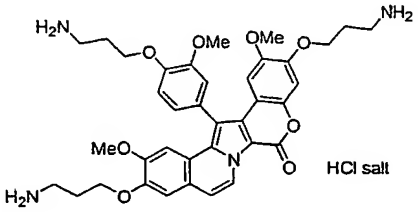
Compound **201**



Gerenal procedure **C** (starting from **200**) to afford **201** as a white solid (110 mg, 85%).

^{1}H NMR (300 MHz, CD_3OD) δ 9.18 (d, J= 7.5 Hz, 1H), 7.47 (d, J= 7.5 Hz, 1H), 7.37 (d, J= 8.0 Hz, 1H), 7.28 (d, J= 1.8 Hz, 1H), 7.23 (dd, J= 8.0, 1.8 Hz, 1H), 7.10 (s, 1H), 7.07 (s, 1H), 6.80 (s, 1H), 4.28 (t, J= 5.7 Hz, 4H), 4.21 (t, J= 5.5 Hz, 2H), 3.91 (s, 3H), 3.88 (s, 6H), 3.47 (s, 3H), 3.46 (s, 3H), 3.30-2.25 (m, 4H), 3.19 (t, J= 7.0 Hz, 2H), 2.30-2.15 (m, 6H).
MS (ESI) m/z: 701 $(M+1)^+$.

Compound **202**



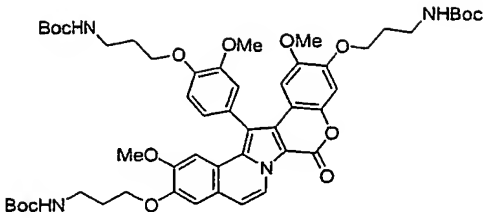
Gerenal procedure **C** (starting from **203**) to afford **202** as a pink solid (80 mg, 80%).

%).

^{1}H NMR (300 MHz, CD_3OD) δ 9.02 (d, J= 7.3 Hz, 1H), 7.40-7.30 (m, 3H), 7.30-7.15 (m, 3H), 6.96 (s, 1H), 6.77 (s, 1H), 4.27 (t, J= 5.7 Hz, 4H), 4.35-4-15 (m, 2H), 3.90 (s, 3H), 3.47 (s, 3H), 3.46 (s, 3H), 3.40-3.20 (m, 6H), 2.20-2.10 (m, 6H), 1.58 (s, 9H), 1.48 (s, 9H), 1.44 (s, 9H).

MS (ESI) m/z: 671 $(M+1)^+$.

Compound **203**

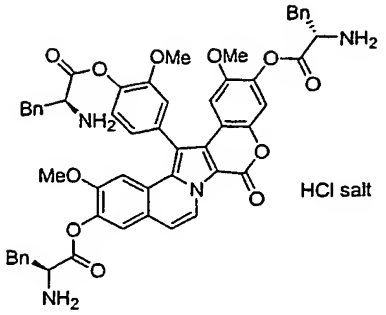


A suspension of **3** (100 mg, 0.20 mmol), Cs_2CO_3 (293 mg, 0.90 mmol) in anhydrous DMF (2 mL) was stirred at 23 °C under argon atmosphere for 30 minutes, then 3-(BOC-amino)propyl bromide (214 mg, 0.90 mmol) was added and the mixture was heated at 40 °C for 4 hours. The resulting solution was cooled to 23 °C, quenched with H_2O, diluted with EtOAc (50 mL) and washed with H_2O (2x20 mL).

The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the solvent removed under vaccum. The residue was purified by chromatography on silica gel (CH_2Cl_2:MeOH, 30:1) to give **203** as a white solid (144 mg, 74%).

^1H NMR (300 MHz, CD_3OD) δ 9.24 (d, J= 7.3 Hz, 1H), 7.25-7.10 (m, 4H), 7.08 (s, 1H), 7.04 (d, J= 7.3 Hz, 1H), 6.93 (s, 1H), 6.72 (s, 1H), 5.50-5.40 (m, 3H), 4.30-4.10 (m, 6H), 3.87 (s, 3H), 3.47 (s, 3H), 3.46 (s, 3H), 3.30-2.10 (m, 6H), 2.30-2.15 (m, 6H).
MS (ESI) m/z: 971 $(M+1)^+$.
Rf: 0.73 (CH_2Cl_2:MeOH, 30:1).

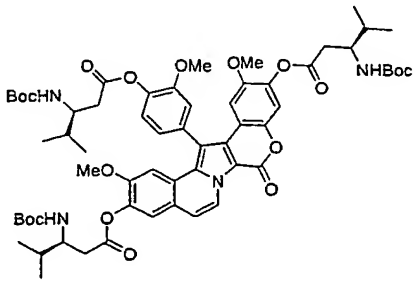
Compound **204**



Gerenal procedure **C** (starting from **113**) to afford **204** as a pale yellow solid (781 mg, 81%).

^{1}H NMR (300 MHz, CD_3OD) δ 9.17 (d, J= 7.3 Hz, 1H), 7.60-7.25 (m, 21H), 7.17 (d, J= 3.1 Hz, 1H), 6.89 (d, J= 3.1 Hz, 1H), 4.80-4.60 (m, 3H), 3.94 (s, 3H), 3.60-3.40 (m, 12H).
MS (ESI) m/z: 941 $(M+1)^+$.

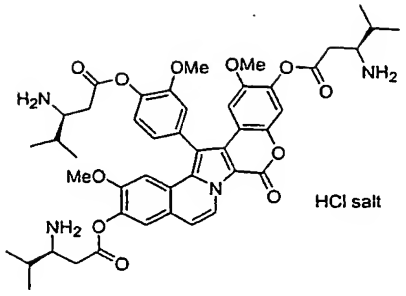
Compound **205**



General procedure **D** (starting from **3** and Boc-L- -Leu-OH) and chromatography on silica gel (hexane:EtOAc, 3:2) to afford **205** as a yellow oil (100 mg, 88%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (d, J= 7.5 Hz, 1H), 7.45 (s, 1H), 7.33 (d, J= 8.0 Hz, 1H), 7.25-7.15 (m, 4H), 7.06 (d, J= 7.5 Hz, 1H), 6.79 (d, J= 7.1 Hz, 1H), 5.10-4.90 (m, 3H), 4.10-3.90 (m, 3H), 3.82 (s, 3H), 3.44 (s, 6H), 2.90-2.70 (m, 6H), 2.00-1.90 (m, 3H), 1.45 (s, 27H), 1.10-0.90 (m, 18H).
MS (ESI) m/z: 1161 $(M+23)^+$.
Rf: 0.17 (hexane:EtOAc, 2:1).

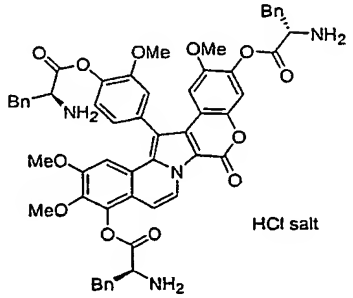
Compound **206**



General procedure **C** (starting from **205**) to afford **206** as a white solid (66 mg, 85%).

^{1}H NMR (300 MHz, CD_3OD) δ 9.23 (d, J= 7.7 Hz, 1H), 7.64 (s, 1H), 7.55-7.45 (m, 2H), 7.40-7.30 (m, 4H), 6.91 (s, 1H), 3.87 (s, 3H), 3.70-3.50 (m, 3H), 3.46 (s, 6H), 3.20-2.90 (m, 6H), 2.20-2.05 (m, 3H); 1.20-1.05 (m, 18H).
MS (ESI) m/z: 839 $(M+1)^+$.

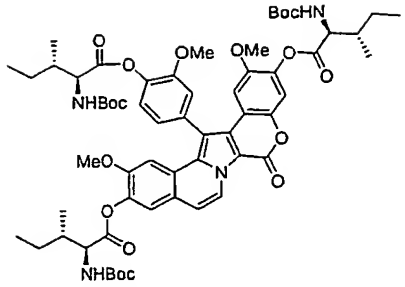
Compound **207**



General procedure **C** (starting from **120**) to afford **207** as a white solid (225 mg, 80%).

^{1}H NMR (300 MHz, CD_3OD) δ 9.09 (d, J= 7.3 Hz, 1H), 7.60-7.30 (m, 18H), 7.20 (s, 1H), 7.13 (s, 1H), 7.12 (s, 1H), 6.87 (d, J= 2.9 Hz, 1H), 4.76 (t, J= 6.6 Hz, 2H), 4.62 (d, J= 6.6 Hz, 1H), 4. 00-3.85 (m, 6H), 3.70-3.35 (m, 12H).
MS (ESI) m/z: 971 $(M+1)^+$.

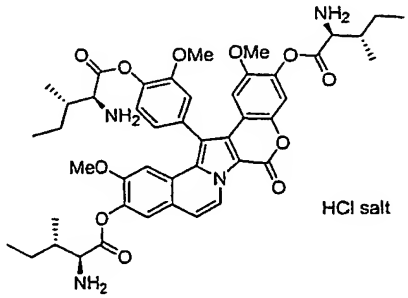
Compound **208**



General procedure **D** (starting from **3** and Boc-L-Ile-OH) and chromatography on silica gel (hexane:EtOAc, 2:1) to afford **208** as a yellow solid (537 mg, 94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (d, J= 7.5 Hz, 1H), 7.42 (s, 1H), 7.35-7.15 (m, 5H), 7.09 (d, J= 7.5 Hz, 1H), 6.79 (d, J= 7.0 Hz, 1H), 5.10-5.05 (m, 3H), 4.60-4.55 (m, 3H), 3.79 (s, 3H), 3.43 (s, 6H), 2.20-2.05 (m, 3H), 1.70-1.60 (m, 3H), 1.49 (s, 9H), 1.47 (s, 9H), 1.45 (s, 9H), 1.40-1.20 (s, 6H), 1.15-0.90 (m, 18H).
MS (ESI) m/z: 1162 $(M+23)^+$.
Rf: 0.45 (hexane:EtOAc, 2:1).

Compound **209**

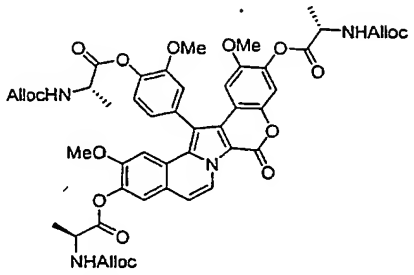


General procedure **C** (starting from **208**) to afford **209** as a white solid (362 mg, 91%).

^{1}H NMR (300 MHz, CD_3OD) δ 9.24 (d, J= 7.5 Hz, 1H), 7.67 (s, 1H), 7.60-7.50 (m, 2H), 7.45-7.30 (m, 4H), 6.92 (d, J= 9.8 Hz, 1H), 4.40 (d, J= 3.4

Hz, 1H), 4.37 (d, *J*= 3.6 Hz, 1H), 4.33 (d, *J*= 3.6 Hz, 1H), 3.88 (s, 3H), 3.49 (s, 3H), 3.48 (s, 6H), 2.30-2.10 (m, 3H), 1.90-1.70 (m, 3H), 1.60-1.40 (m, 3H), 1.30-1.00 (m, 18H).
MS (ESI) m/z: 839 $(M+1)^+$.

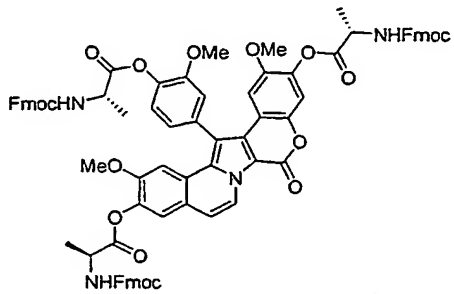
Compound **210**



General procedure **D** (starting from **3** and Alloc-Ala-OH) and chromatography on silica gel (CH_2Cl_2:MeOH, 80:1) to afford **210** as a white solid (29 mg, 74%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.15-9.05 (m, 1H), 7.40-7.20 (m, 4H), 7.17 (d, *J*= 6.5 Hz, 1H), 7.07 (s, 1H), 6.95-6.85 (m, 1H), 6.77 (d, *J*= 5.8 Hz, 1H), 6.00-5.80 (m, 3H), 5.50-5.20 (m, 9H), 4.80-4.50 (m, 9H), 3.84 (d, *J*= 2.9 Hz, 3H), 3.44 (s, 6H), 1.70-1.50 (m, 9H).
Rf: 0.14 (CH_2Cl_2:MeOH, 80:1).

Compound **211**



To a suspension of **3** (20 mg, 0.04 mmol), Fmoc-Ala-OH (93 mg, 0.30 mmol) in CH_2Cl_2 anh. (2 mL) under Argon atmosphere at 0 °C was

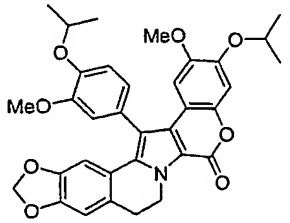
added HATU (114 mg, 0.30 mmol) and N-Methylmorpholine (0.053 mL, 0.48 mmol).

The mixture was stirred at 23 °C overnight. The resulting pale brown solution was diluted with CH_2Cl_2 (20 mL), washed with $KHCO_3$ 10% (20 mL), saturated aqueous solution of Na_2SO_4 (20 mL), and brine (20 mL).

The organic phase was dried over anhydrous Na_2SO_4 and the solvent removed under vaccum. The residue was purified by chromatography on silica gel (CH_2Cl_2:MeOH, 100:1) to give **211** as a white solid (32 mg, 84%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (d, *J*= 7.7 Hz, 1H), 7.80-7.70 (m, 6H), 7.65-7.55 (m, 6H), 7.50-7.25 (m, 15H), 7.25-7.15 (m, 3H), 7.19 (d, *J*= 6.9 Hz, 1H), 6.80-6.75 (m, 1H), 5.45-5.35 (m, 3H), 4.80-4.65 (m, 3H), 4.50-4.40 (m, 6H), 4.30-4.20 (m, 3H), 3.81 (s, 3H), 3.43 (s, 6H), 1.75-1.55 (m, 9H).
MS (ESI) m/z: 1401 $(M+23)^+$.
Rf: 0.15 (CH_2Cl_2:MeOH, 100:1).

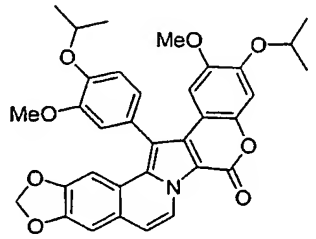
Compound **212**



General procedure **H** (starting from 6,7-methylendioxi-3,4-dihidroisoquinoline) and chromatography on silica gel Merck-60 (230-400 mesh) (5:5:2 hexane-DCM-Et_2O) to provide **212** as a yellow solid (144 mg, 66%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10-6.95 (m, 3H), 6.90 (s, 1H), 6.74 (s, 1H), 6.62 (s, 1H), 6.58 (s, 1H), 5.89 (s, 2H), 4.80-4.50 (m, 4H), 3.82 (s, 3H), 3.41 (s, 3H), 3.08 (t, J= 6.5 Hz, 2H), 1.50-1.25 (m, 12H).
MS (ESI) m/z: 588.2 $(M+5)^+$.
Rf: 0.27 (hexane:EtOAc, 1:1).

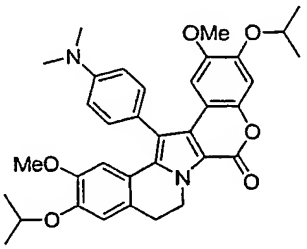
Compound **213**



General procedure **E** (starting from **212**, reaction time 3 h) and chromatography on silica gel (hexane:EtOAc, 1:1) to give **213** (19 mg, 33%).

^{1}H NMR (300 MHz, $CDCl_3$) δ9.23 (d, J= 6.5 Hz, 1H), 7.20-6.90 (m, 7H), 6.63 (s, 1H), 6.00-5.95 (m, 2H), 4.80-4.50 (m, 2H), 3.83 (s, 3H), 3.43 (s, 3H), 1.50-1.20 (m, 12H).
MS (ESI) m/z: 582.2 $(M+1)^+$.
Rf: 0.48 (hexane:EtOAc, 1:1).

Compound **214**



General procedure **M** (starting from 4-dimethylaminophenyl boronic acid) and chromatography on silica gel (Hexane:EtOAc 3:1 to 2:1) to provide **214** (13 mg, 28%).

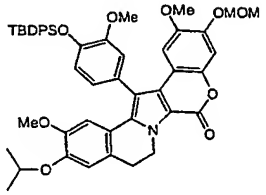
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 2H), 6.89 (m, 3H), 6.76 (m, 3H), 4.78 (t, J= 6.7 Hz, 2H), 4.54 (m, 2H), 3.44 (s, 3H), 3.33 (s, 3H), 3.08 (t, J= 6.7 Hz, 2H), 2.98 (s, 6H), 1.37 (d, J= 6.2 Hz, 6H), 1.36 (d, J= 6.2 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ155.8, 150.5, 148.6, 147.2, 146.9, 146.6, 145.9, 136.2, 131.9, 128.5, 126.3, 123.0, 120.6, 115.5, 114.7, 113.7, 113.4, 110.8, 109.4, 105.2, 103.6, 71.5, 71.4, 55.6, 55.2, 42.4, 40.8, 29.3, 28.7, 22.1, 21.9.

MS (ESI) m/z: 583.5 $(M+1)^+$.

Rf: 0.50 (hexane:EtOAc, 1:1).

Compound **215**



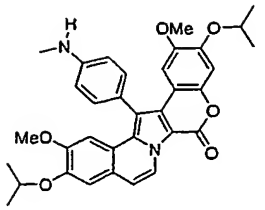
General procedure **H** (starting from 6-isopropoxy-7-methoxy-3,4-dihydroisoquinoline) and chromatography on silica gel (Hexane:CH_2Cl_2:Et_2O 5:5:2) to provide **215** as white solid (21 mg, 21%).

^{1}H NMR (300 MHz, $CDCl_3$) δ7.73 (m, 4H), 7.44-7.35 (m, 6H), 7.20 (s, 1H), 6.94-6.80 (m, 3H), 6.75 (s, 1H), 6.71 (s, 1H), 6.67 (s, 1H), 5.23 (s, 2H), 4.84 (m, 1H), 4.68 (m, 1H), 4.56 (hp, J= 6.0 Hz, 1H), 3.60 (s, 3H), 3.49 (s, 3H), 3.40 (s, 3H), 3.31 (s, 3H), 3.06 (m, 2H), 1.37 (d, J= 6.0 Hz, 6H), 1.13 (s, 9H).

MS (ESI) m/z: 826.3 $(M+1)^+$.

Rf: 0.40 (Hexane/CH_2Cl_2/Et_2O 5:5:2).

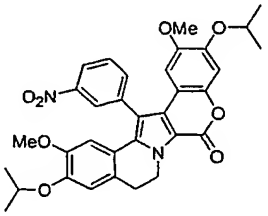
Compound **216**



General procedure **E** (starting from **214**, reaction time 6 h) and chromatography on silica gel (Hexane:EtOAc 1:1) to provide **216** (8 mg, 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ9.21 (d, J= 7.3 Hz, 1H), 7.39 (m, 2H), 7.30 (s, 1H), 7.08 (s, 1H), 7.00 (d, J= 7.3 Hz, 1H), 6.96 (s, 1H), 6.84 (m, 3H), 4.69 (hp, J= 6.2 Hz, 1H), 4.57 (hp, J= 6.2 Hz, 1H), 3.48 (s, 3H), 3.47 (s, 3H), 2.92 (s, 3H), 1.43 (d, J= 6.2 Hz, 6H), 1.40 (d, J= 6.2 Hz, 6H).
MS (ESI) m/z: 867.4 $(M+1)^+$.
Rf: 0.25 (Hexane:EtOAc 1:1).

Compound **217**



General procedure **M** (starting from 3-nitrophenyl boronic acid) and chromatography on silica gel (Hexane:EtOAc 2:1) to provide **217** (33 mg, 67%) and LLSA-3,4-di(OiPr)-14(I) (10 mg, 20%).

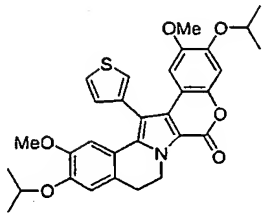
^{1}H NMR (300 MHz, $CDCl_3$) δ8.45 (s, 1H), 8.35 (d, J= 8.1 Hz, 1H), 7.96 (d, J= 7.7 Hz, 1H), 7.78 (dd, J= 7.7, 8.1 Hz, 1H), 6.92 (s, 1H), 6.79 (s, 1H), 6.44 (s, 1H), 6.36 (s, 1H), 4.80 (dt, J= 6.5, 6.3 Hz, 2H), 4.55 (m, 2H), 3.37 (s, 3H), 3.24 (s, 3H), 3.10 (t, J= 6.5 Hz, 2H), 1.37 (d, J= 6.1 Hz, 6H), 1.36 (d, J= 6.1 Hz, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 148.9, 148.6, 148.0, 147.6, 146.7, 146.2, 138.2, 137.9, 136.1, 130.1, 127.8, 127.1, 126.4, 122.7, 119.3,

115.0, 114.3, 112.0, 109.7, 109.2, 104.6, 103.9, 71.6, 71.5, 55.6, 55.2, 42.5, 29.7, 22.0, 21.8 .

MS (ESI) m/z: 585.4 $(M+1)^+$.

Rf: 0.60 (Hexane:EtOAc 1:1).

Compound **218**



General procedure **M** (starting from 3-thiopheneboronic acid) and chromatography on silica gel (Hexane:EtOAc 2:1) to provide **218** (18 mg, 39%).

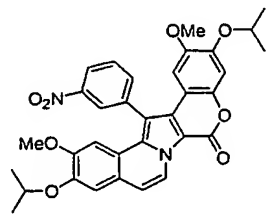
^{1}H NMR (300 MHz, $CDCl_3$) δ7.60 (dd, *J*= 3.1, 5.0 Hz, 1H), 7.44 (dd, *J*= 1.3, 3.1 Hz, 1H), 7.26 (dd, *J*= 1.3, 5.0 Hz, 1H), 6.91 (s, 1H), 6.76 (s, 1H), 6.71 (s, 1H), 6.63 (s, 1H), 4.77 (m, 2H), 4.54 (m, 2H), 3.50 (s, 3H), 3.41 (s, 3H), 3.09 (t, *J*= 6.6 Hz, 2H), 1.38 (d, *J*= 6.0 Hz, 6H), 1.37 (d, *J*= 6.0 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 148.7, 147.4, 147.0, 146.6, 145.9, 136.5, 135.5, 130.3, 128.8, 126.9, 126.3, 125.2, 120.0, 114.5, 113.9, 110.3, 108.9, 108.7, 104.4, 103.4, 71.4, 71.3, 55.4, 55.1, 42.4, 29.7, 28.6, 22.0, 21.8 .

MS (ESI) m/z: 546.5 $(M+1)^+$.

Rf: 0.65 (Hexane:EtOAc 1:1).

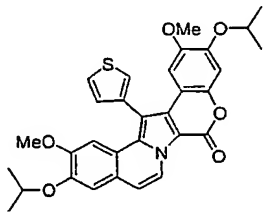
Compound **219**



General procedure **E** (starting from **217**, reaction time 5 h) and chromatography on silica gel (Hexane:EtOAc 2:1) to provide **219** (26 mg, quantitative).

^{1}H NMR (300 MHz, $CDCl_3$) δ9.27 (d, J= 7.4 Hz, 1H), 8.56 (m, 1H), 8.43 (m, 1H), 8.07 (d, J= 7.7 Hz, 1H), 7.88 (dd, J= 7.7, 8.0 Hz, 1H), 7.12 (s, 1H), 7.07 (d, J= 7.4 Hz, 1H), 6.97 (s, 1H), 6.84 (s, 1H), 6.45 (s, 1H), 4.70 (hp, J= 6.1 Hz, 1H), 4.57 (hp, J= 6.1 Hz, 1H), 3.37 (s, 3H), 3.34 (s, 3H), 1.42 (d, J= 6.1 Hz, 6H), 1.39 (d, J= 6.1 Hz, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 150.5, 149.0, 148.4, 148.9, 146.8, 146.7, 138.7, 138.5, 134.1, 130.3, 129.2, 127.0, 125.1, 123.2, 123.1, 118.3, 112.9, 110.8, 109.2, 108.5, 108.0, 105.1, 103.8, 71.6, 71.4, 55.5, 55.1, 29.7, 21.9, 21.8.
MS (ESI) m/z: 583.2 $(M+1)^+$.
Rf: 0.60 (Hexane:EtOAc 1:1).

Compound **220**



General procedure **E** (starting from **218**, reaction time 5 h) and chromatography on silica gel (Hexane:EtOAc 2:1) to provide **220** (13 mg, 99%).

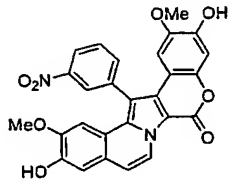
^{1}H NMR (300 MHz, $CDCl_3$) δ9.20 (d, J= 7.4 Hz, 1H), 7.70 (dd, J= 3.0, 4.8 Hz, 1H), 7.56 (dd, J= 1.3, 3.0 Hz, 1H), 7.34 (dd, J= 1.3, 4.8 Hz, 1H), 7.16 (s, 1H), 7.09 (s, 1H), 7.02 (d, J= 7.4 Hz, 1H), 6.96 (s, 1H), 6.71 (s, 1H), 4.70 (hp, J= 6.2 Hz, 1H), 4.57 (d, J= 6.2 Hz, 1H), 3.52 (s, 6H), 1.43 (d, J= 6.2 Hz, 6H), 1.40 (d, J= 6.2 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 150.2, 148.5, 147.9, 146.6, 135.8, 134.8, 130.8, 130.0, 127.2, 125.9, 124.7, 123.2, 118.9, 112.4, 110.3, 109.8, 108.1, 105.2, 104.9, 103.3, 71.4, 71.2, 55.4, 55.1, 29.7, 21.9, 21.8 .

MS (ESI) m/z: 544.2 $(M+1)^+$.

Rf: 0.65 (Hexane:EtOAc 1:1).

Compound **221**



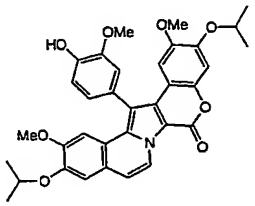
General procedure **A** (starting from **219**) and chromatography on silica gel (CH_2Cl_2:MeOH 50:1) to provide **221** (14 mg, 88%).

^1H NMR (300 MHz, $CDCl_3/CD_3OD$) δ9.14 (d, J= 7.3 Hz, 1H), 8.52 (m, 1H), 8.46 (d, J= 8.4 Hz, 1H), 8.08 (d, J= 7.9 Hz, 1H), 7.92 (dd, J= 7.9, 8.4 Hz, 1H), 7.14 (s, 1H), 7.06 (d, J= 7.3 Hz, 1H), 6.90 (s, 1H), 6.82 (s, 1H), 6.42 (s, 1H), 3.37 (s, 3H), 3.36 (s, 3H).

MS (ESI) m/z: 499.4 $(M+1)^+$.

Rf: 0.15 (CH_2Cl_2:MeOH 50:1).

Compound **222**

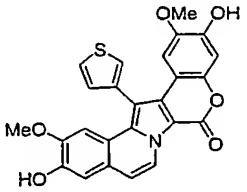


A suspension of **3** (50 mg, 0.10 mmol) and Cs_2CO_3 (34mg, 0.105 mmol) in anhydrous DMF (2 mL) under Argon atmosphere was heated at 40 °C for 30 minutes. Isopropylmagnesium bromide (0.014 mL, 0.15mmol) was added dropwise via syringe to the reaction mixture. The resulting yellow suspension was stirred at 40 °C for 16 hours. The reaction

mixture was cooled to 23 °C and evaporated in vacuo. The residue was disolved in CH_2Cl_2, filtered, and the solvent removed under vacuum. The residue was purified by chromatography on silica gel (hexane:EtoAc 2:1 to 1:1) to afford **222** (30 mg, 51%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.21 (d, J= 7.3 Hz, 1H), 7.28-7.08 (m, 5H), 7.01 (d, J= 7.3 Hz, 1H), 6.96 (s, 1H), 6.74 (s, 1H), 5.89 (s, 1H), 4.69 (hp, J= 6.0 Hz, 1H), 4.57 (hp, J= 6.2 Hz, 1H), 3.88 (s,3H), 3.46 (s, 3H), 3.45 (s, 3H), 1.43 (d, J= 6.0 Hz, 6H), 1.40 (d, J= 6.2 Hz, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 150.2, 148.5, 147.9, 147.3, 146.6, 145.7, 134.4, 129.5, 124.7, 123.1, 119.0, 115.2, 113.9, 112.3, 111.1, 110.5, 110.0, 107.8, 105.7, 105.6, 103.5, 71.4, 71.2, 56.2, 55.5, 55.2, 29.7, 21.9, 21.8 .
MS (ESI) m/z: 584.2 $(M+1)^+$.
Rf: 0.40 (Hexane/EtOAc 1:1).

Compound **223**

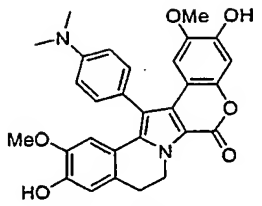


General procedure **A** (starting from **220**) and chromatography on silica gel (Hexane/EtOAc 1:1) to provide **223** (1.5 mg, 38%).

^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$) δ 9.06 (d, J= 7.4 Hz, 1H), 7.70 (dd, J= 3.0, 4.8 Hz, 1H), 7.53 (dd, J= 1.3, 3.0 Hz, 1H), 7.30 (dd, J= 1.3, 4.8 Hz, 1H), 7.10 (s, 1H), 7.09 (s, 1H), 6.98 (d, J= 7.4 Hz, 1H), 6.90 (s, 1H), 6.63 (s, 1H), 3.52 (s, 3H), 3.51 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$) δ 156.4, 148.6, 148.1, 147.5, 147.0, 144.9, 136.1, 135.8, 130.9, 130.8, 127.6, 126.2, 125.7, 123.1, 118.7, 112.7, 111.4, 109.6, 107.9, 105.2, 105.0, 102.9, 102.8, 55.5, 55.2 .
MS (ESI) m/z: 460.0 $(M+1)^+$.

Rf: 0.20 (CH_2Cl_2:MeOH 50:1).

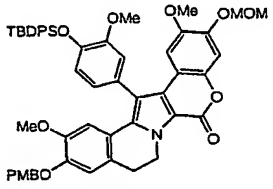
Compound **224**



General procedure **A** (starting from **214**) and chromatography on silica gel (CH_2Cl_2:MeOH 50:1 to 20:1) to provide **224** (11mg, 50%).

^{1}H NMR (500 MHz, $CDCl_3/CD_3OD$) δ 7.43 (s, 1H), 7.31 (m, 2H), 6.91 (m, 2H), 6.81 (s, 1H), 6.72 (s, 1H), 6.70 (s, 1H), 4.67 (t, J= 6.7 Hz, 2H), 3.43 (s, 3H), 3.33 (s, 3H), 3.02 (t, J= 6.7 Hz, 2H), 2.96 (s, 6H).
^{13}C NMR (125 MHz, $CDCl_3/CD_3OD$) δ 156.9, 151.1, 146.8, 146.6, 146.5, 146.4, 145.0, 137.5, 132.3, 129.7, 127.6, 123.6, 119.8, 115.4, 115.1, 114.0, 113.4, 110.5, 109.6, 105.3, 103.9, 55.7, 55.4, 42.8, 41.1, 28.7 .
MS (ESI) m/z: 499.2 $(M+1)^+$.
Rf: 0.15 (CH_2Cl_2:MeOH 40:1).

Compound **225**

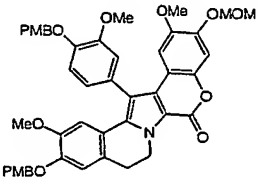


A suspension of **227** (63 mg, 0.080 mmol) and Cs_2CO_3 (29 mg, 0.088 mmol) in anhydrous DMF under Argon atmosphere at room temperature for 30 minutes. 4-methoxybenzyl chloride (0.088 mmol) was added dropwise via syringe to the reaction mixture. The resulting suspension was stirred at room temperature overnight. The progress of the reaction was followed by TLC (CH_2Cl_2/EtOAc 10:1). The reaction mixture was evaporated in vacuo. The residue was purified by

chromatography on silica gel (CH_2Cl_2/EtOAc 10:1) to obtain **225** (9 mg, 12%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (m, 4H), 7.46-7.35 (m, 8H), 7.34 (s, 1H), 6.93-6.80 (m, 5H), 6.76 (s, 1H), 6.71 (s, 1H), 6.67 (s, 1H), 5.65 (s, 1H), 5.22 (s, 2H), 5.08 (s, 2H), 4.82 (m, 1H), 4.63 (m, 1H), 3.81 (s, 3H), 3.60 (s, 3H), 3.49 (s, 3H), 3.40 (s, 3H), 3.32 (s, 3H), 3.04 (m, 2H), 1.13 (s, 9H).
MS (ESI) m/z: 904.0 $(M+1)^+$.
Rf: 0.65 (CH_2Cl_2/EtOAc 10:1).

Compound **226**

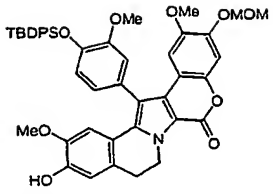


A suspension of **227** (63 mg, 0.080 mmol) and Cs_2CO_3 (29 mg, 0.088 mmol) in anhydrous DMF under Argon atmosphere at room temperature for 30 minutes. 4-methoxybenzyl chloride (0.088 mmol) was added dropwise via syringe to the reaction mixture. The resulting suspension was stirred at room temperature overnight. The progress of the reaction was followed by TLC (CH_2Cl_2/EtOAc 10:1).The reaction mixture was evaporated in vacuo. The residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc 10:1) to obtain **226** (33 mg, 48%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.33 (m, 8H), 7.25 (s, 1H), 7.21-7.00 (m, 3H), 6.92-6.88 (m, 4H), 6.77 (s, 1H), 6.69 (s, 1H), 6.64 (s, 1H), 5.22 (s, 2H), 5.19 (s, 2H), 5.07 (s, 2H), 4.82 (m, 1H), 4.64 (m, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.49 (s, 3H), 3.36 (s, 3H), 3.27 (s, 3H), 3.05 (m, 2H).
MS (ESI) m/z: 786.0 $(M+1)^+$.

Rf: 0.50 (CH_2Cl_2/EtOAc 10:1).

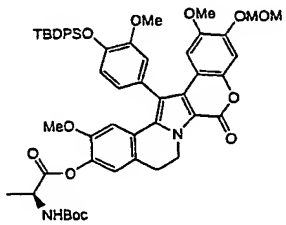
Compound **227**



General procedure **G** (starting from 6-hydroxy-7-methoxy-3,4-dihydroisoquinoline and iodo-acetic acid 2-[4-(tert-butyl-diphenyl-silannyloxy)-3-methoxy-phenylethynyl]-4-methoxy-5-methoxymethoxy-phenyl ester) and chromatography on silica gel (Hexane:CH_2Cl_2:Et_2O 5:5:2) to provide **227** slightly impure (103 mg, 20%). To obtain a pure product, this compound was submitted to chromatography on LiChroprep® NH_2 (EtOAc) (24 mg, 5%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (m, 4H), 7.47-7.35 (m, 6H), 7.20 (s, 1H), 6.94-6.70 (m, 4H), 6.67 (m, 2H), 5.65 (s, 1H), 5.23 (s, 2H), 4.84 (m, 1H), 4.63 (m, 1H), 3.61 (s, 3H), 3.49 (s, 3H), 3.40 (s, 3H), 3.36 (s, 3H), 3.05 (m, 2H), 1.14 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 151.1, 146.1, 145.9, 145.8, 145.7, 145.1, 144.9, 135.9, 135.1, 133.5, 133.4, 129.9, 128.3, 127.6, 127.4, 123.3, 120.3, 119.6, 115.1, 114.8, 114.1, 113.8, 111.9, 108.4, 105.3, 105.0, 95.5, 56.2, 55.7, 55.4, 55.3, 42.3, 29.6, 28.4, 26.7, 19.8 . MS (APCI) m/z: 784.1 $(M+1)^+$.
Rf: 0.25 (CH_2Cl_2/MeOH 100:1).

Compound **228**

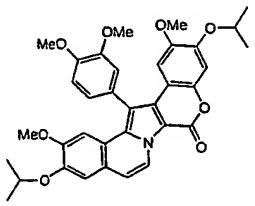


A suspension of **227** (25 mg, 0.031 mmol), Boc-L-Ala-OH (12 mg, 0.063 mmol), EDC·HCl (12 mg, 0.063 mmol) and DMAP (0.8 mg, 0.0063 mmol) in CH_2Cl_2 anh. (2 mL) was stirred under argon atmosphere at room temperature for 2h. The resulting solution was diluted with CH_2Cl_2 (20 mL), washed with water (20 mL) and saturated $NaHCO_3$ aqueous solution (20 mL).

The organic phase was dried over anhydrous sodium sulfate and the solvent removed under vaccum to give **228** as a white solid (30 mg, quant.).

^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (m, 4H), 7.44-7.35 (m, 6H), 7.20 (s, 1H), 6.96-6.80 (m, 5H), 6.65 (s, 1H), 5.22 (s, 2H), 5.09 (m, 1H), 4.90 (m, 1H), 4.63 (m, 1H), 3.61 (s, 3H), 3.49 (s, 3H), 3.39 (s, 3H), 3.27 (s, 3H), 3.07 (m, 2H), 1.55 (d, J= 7.2 Hz, 3H), 1.47 (s, 9H), 1.13 (s, 9H).
MS (ESI) m/z: 955.2 $(M+1)^+$.
Rf: 0.65 (Hexane / EtOAc 1:1).

Compound **229**

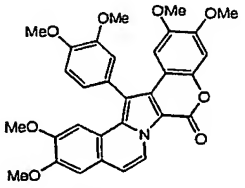


A suspension of **222** (25 mg, 0.043 mmol) and Cs_2CO_3 (21mg, 0.064 mmol) in anhydrous DMF under Argon atmosphere was heated at 40 °C for 30 minutes. MeI (0.215mmol) was added dropwise via syringe to the reaction mixture. The resulting yellow suspension was stirred at 40 °C for 3 hours. The progress of the reaction was followed by TLC (CH_2Cl_2/MeOH 8:0.2).

The reaction mixture was cooled to 23 °C and evaporated in vacuo. The residue was disolved in CH_2Cl_2, filtered, and the solvent removed under vacuum to afford **229** (22 mg, 85%).

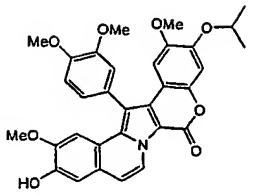
^{1}H NMR (500 MHz, DMSO-d_6) δ 9.07 (d, J= 7.4 Hz, 1H), 7.46 (s, 1H), 7.33 (d, J= 7.4 Hz, 1H), 7.28 (d, J= 8.2 Hz, 1H), 7.21 (d, J= 2.5 Hz, 1H), 7.16 (dd, J= 8.2, 2.5 Hz, 1H), 7.15 (s, 1H), 7.11 (s, 1H), 6.70 (s, 1H), 4.76 (hp, J= 6.1 Hz, 1H), 4.69 (hp, J= 6.1 Hz, 1H), 3.86 (s,3H), 3.75 (s, 3H), 3.34 (s, 3H), 3.32 (s, 3H), 1.31 (d, J= 6.1 Hz, 3H), 1.30 (d, J= 6.1 Hz, 3H), 1.27 (d, J= 6.1 Hz, 3H), 1.26 (d, J= 6.1 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 150.1, 149.8, 149.0, 148.5, 147.9, 146.6, 146.5, 134.4, 129.5, 128.3, 124.7, 124.1, 123.2, 118.9, 114.3, 112.3, 111.9, 110.9, 110.3, 109.9, 107.8, 105.6, 105.4, 103.4, 71.4, 71.1, 56.3, 56.1, 55.5, 55.2, 29.7, 21.9, 21.8 .
MS (ESI) m/z: 598.4 $(M+1)^+$.
Rf: 0.65 (CH_2Cl_2/MeOH 8:0.2).

Compound **230**



This compound is a by-product of the synthesis of **222**.
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (d, J= 7.5 Hz, 1H), 7.28-7.11 (m, 4H), 7.10 (s, 1H), 7.07 (d, J= 7.5 Hz, 1H), 6.97 (s, 1H), 6.74 (s, 1H), 3.99 (s, 6H), 3.92 (s, 3H), 3.88 (s, 3H), 3.47 (s, 3H), 3.46 (s, 3H).
MS (APCI) m/z: 842.2 $(M+1)^+$.
Rf: 0.35 (CH_2Cl_2/MeOH 9:0.2).

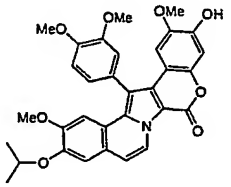
Compound **231**



A suspension of **222** (22 mg, 0.037 mmol) and $AlCl_3$ (12 mg, 0.092 mmol) in anhydrous CH_2Cl_2 (1 mL) was stirred at room temperature for 2'5 h under Argon atmosphere. CH_2Cl_2 and MeOH were added and then the solvent was evaporated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2/MeOH 9:0.5) to provide **231** (3 mg, 15%).

^1H NMR (500 MHz, DMSO-d_6) δ 9.98 (s, 1H), 9.03 (d, J= 7.4 Hz, 1H), 7.29 (d, J= 8.2 Hz, 1H), 7.25 (d, J= 7.4 Hz, 1H), 7.21 (d, J= 2.5 Hz, 1H), 7.20 (s, 1H), 7.16 (dd, J= 8.2, 2.5 Hz, 1H), 7.14 (s, 1H), 7.10 (s, 1H), 6.69 (s, 1H), 4.69 (hp, J= 6.1 Hz, 1H), 3.86 (s, 3H), 3.76 (s, 3H), 3.37 (s, 3H), 3.35 (s, 3H), 1.27 (d, J= 6.1 Hz, 3H), 1.26 (d, J= 6.1 Hz, 3H).
^{13}C NMR (125 MHz, DMSO-d_6) δ 154.3, 149.9, 149.0, 148.6, 148.4, 147.5, 146.2, 146.1, 134.0, 128.6, 127.1, 124.7, 123.6, 122.0, 117.5, 114.6, 113.0, 112.6, 111.6, 110.7, 109.2, 106.7, 105.2, 103.2, 70.5, 56.0, 55.8, 54.8, 54.5, 29.0, 21.7, 21.6 . MS (APCI) m/z: 556.1 $(M+1)^+$.
Rf: 0.30 (CH_2Cl_2/MeOH 9:0.2).

Compound **232**

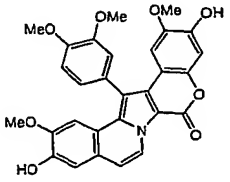


A suspension of **222** (22 mg, 0.037 mmol) and $AlCl_3$ (12 mg, 0.092 mmol) in anhydrous CH_2Cl_2 (1 mL) was stirred at room temperature for 2'5 h under Argon atmosphere. CH_2Cl_2 and MeOH were added and then the solvent was evaporated under reduced pressure. The residue was

purified by preparative TLC (CH_2Cl_2/MeOH 9:0.5) to provide **232** (1 mg, 5%).

^1H NMR (500 MHz, DMSO-d_6) δ 9.88 (s, 1H), 9.06 (d, J= 7.4 Hz, 1H), 7.46 (s, 1H), 7.30 (d, J= 8.2 Hz, 1H), 7.29 (d, J= 7.4 Hz, 1H), 7.21 (d, J= 2.5 Hz, 1H), 7.16 (dd, J= 8.2, 2.5 Hz, 1H), 7.10 (s, 1H), 6.88 (s, 1H), 6.68 (s, 1H), 4.76 (hp, J= 6.1 Hz, 1H), 3.86 (s,3H), 3.76 (s, 3H), 3.36 (s, 3H), 3.32 (s, 3H), 1.31 (d, J= 6.1 Hz, 3H), 1.30 (d, J= 6.1 Hz, 3H).
MS (APCI) m/z: 556.1 $(M+1)^+$.
Rf: 0.25 (CH_2Cl_2/MeOH 9:0.2).

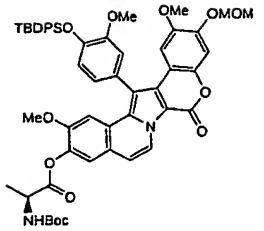
Compound **233**



A suspension of **222** (22 mg, 0.037 mmol) and $AlCl_3$ (12 mg, 0.092 mmol) in anhydrous CH_2Cl_2 (1 mL) was stirred at room temperature for 2'5 h under Argon atmosphere. CH_2Cl_2 and MeOH were added and then the solvent was evaporated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2/MeOH 9:0.5) to provide **233** (5 mg, 26%).

^1H NMR (500 MHz, DMSO-d_6) δ9.97 (s, 1H), 9.86 (s, 1H), 9.02 (d, J= 7.4 Hz, 1H), 7.29 (d, J= 8.2 Hz, 1H), 7.23 (d, J= 7.4 Hz, 1H), 7.21 (d, J= 2.5 Hz, 1H), 7.20 (s, 1H), 7.16 (dd, J= 8.2, 2.5 Hz, 1H), 7.09 (s, 1H), 6.87 (s, 1H), 6.67 (s, 1H), 3.86 (s, 3H), 3.76 (s, 3H), 3.36 (s, 3H), 3.35 (s, 3H).
^{13}C NMR (125 MHz, DMSO-d_6) δ 154.3, 149.9, 149.0, 148.5, 148.3, 147.8, 146.3, 144.6, 134.0, 128.9, 127.3, 124.7, 123.6, 122.0, 117.4, 114.6, 113.1, 112.4, 111.5, 110.4, 108.2, 106.4, 105.6, 105.3, 103.7, 56.0, 55.8, 55.0, 54.5 . MS (APCI) m/z: 514.1 $(M+1)^+$.
Rf: 0.15 (CH_2Cl_2/MeOH 9:0.2).

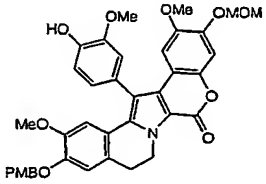
Compound **234**



General procedure **E** (starting from **228**, reaction time 28 h) and chromatography on silica gel (hexane:EtOAc 2:1) to afford **234** as a white solid (24 mg, 81%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.20 (d, J= 7.3 Hz, 1H), 7.75 (d, J= 6.7 Hz, 4H), 7.48-7.37 (m, 6H), 7.25 (s, 1H), 7.03 (s, 1H), 7.00 (d, J= 7.3 Hz, 1H), 6.92 (s, 2H), 6.73 (s, 1H), 5.24 (s, 2H), 5.12 (m, 1H), 4.62 (m, 1H), 3.64 (s, 3H), 3.50 (s, 3H), 3.43 (s, 3H), 3.37 (s, 3H), 1.58 (d, J= 7.0 Hz, 3H), 1.25 (s, 9H), 1.15 (s, 9H).
MS (APCI) m/z: 953.2 $(M+1)^+$.
Rf: 0.25 (hexane/EtAcO, 2:1).

Compound **235**

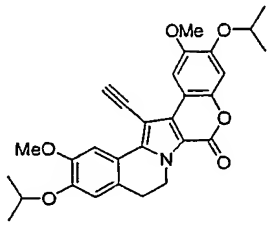


A suspension of **227** (63 mg, 0.080 mmol) and Cs_2CO_3 (29 mg, 0.088 mmol) in anhydrous DMF under Argon atmosphere at room temperature for 30 minutes. 4-methoxybenzyl chloride (0.088 mmol) was added dropwise via syringe to the reaction mixture. The resulting suspension was stirred at room temperature overnight. The progress of the reaction was followed by TLC (CH_2Cl_2/EtOAc 10:1).

The reaction mixture was evaporated in vacuo. The residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc 10:1) to obtain **235** (15 mg, 26%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 2H), 7.22 (s, 1H), 7.14-7.06 (m, 2H), 6.98-6.88 (m, 3H), 6.78 (s, 1H), 6.72 (s, 1H), 6.69 (s, 1H), 5.76 (s, 1H), 5.22 (s, 2H), 5.09 (s, 2H), 4.82 (m, 1H), 4.64 (m, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.49 (s, 3H), 3.47 (s, 3H), 3.37 (s, 3H), 3.05 (m, 2H).
MS (ESI) m/z: 664.4 $(M+1)^+$.
Rf: 0.30 ($CH2Cl_2$/EtOAc 10:1).

Compound **236**



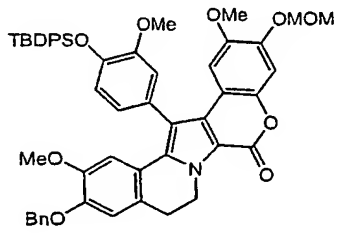
To a stirred solution of **189** (80 mg, 0.135 mmol), $PdCl_2(PPh_3)_2$ (5 mg, 0.006 mmol) and CuI (8 mg, 0.04 mmol) in 5:1 DMF-Et_3N (1.2 mL) under argon atmosphere at room temperature, trimethylsilylacetylene (0.04 mL, 0.27 mmol) was added via syringe. The reaction mixture was heated in a sealed tube at 90°C for 5 hours, then the mixture was cooled to room temperature and quenched with water (10 mL). The mixture was diluted with ethyl acetate (20 mL) and washed with water (2 x 10 mL) and brine (2 x 10 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure.

To a solution of the resulting oil in methanol/dichloromethane (3:2, 5 mL)), potassium carbonate (20 mg, 0.142 mmol) was added in portions at room temperature under argon atmosphere. After 2 hours, a saturated aqueous solution of NH_4Cl was added. The aqueous phase was extracted with CH_2Cl_2 (twice, 20 mL) and the organic phase was

dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel (Hexane/EtOAc 2:1) to obtain **236** (20 mg, 26%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.16 (s, 1H), 6.91 (s, 1H), 6.80 (s, 1H), 4.71 (t, J= 6.6 Hz, 2H), 4.60 (m, 2H), 3.92 (s, 6H), 3.64 (s, 1H), 3.06 (t, J= 6.6 Hz, 2H), 1.41 (d, J= 6.0 Hz, 12H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 149.4, 148.6, 148.2, 147.2, 146.3, 141.7, 131.5, 126.7, 119.8, 114.8, 114.0, 110.4, 109.6, 105.3, 103.4, 82.9, 79.9, 71.7, 56.5, 56.3, 42.7, 28.5, 22.3, 22.1 .
MS (ESI) m/z: 488.5 $(M+1)^+$.
Rf: 0.45 (Hexane/EtOAc 2:1).

Compound **237**



General Procedure **H** (starting from iodo-acetic acid 2-[4-(tert-butyl-diphenyl-silannyloxy)-3-methoxy-phenylethynyl]-4-methoxy-5-methoxymethoxy-phenyl ester and 6-Benzyloxy-7-methoxy-3,4-dihydroisoquinoline) and chromatography on silica gel (5:5:2 hexane-dichloromethane-ether) to afford **237** as a white solid (273 mg, 20%).

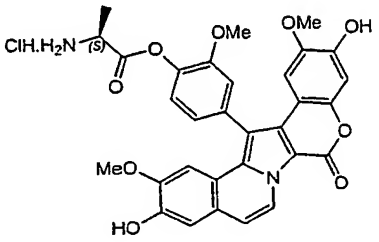
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (m, 4H), 7.45-7.30 (m, 14H), 7.20 (s, 1H), 6.94 (m, 1H), 6.84 (m, 1H), 6.74 (m, 1H), 6.68 (s, 1H), 5.23 (s, 2H), 5.16 (s, 2H), 4.82 (m, 1H), 4.64 (m, 1H), 3.61 (s, 3H), 3.50 (s, 3H), 3.41 (s, 3H), 3.35 (s, 3H), 3.03 (m, 2H), 1.14 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 151.1, 148.1, 146.1, 145.9, 145.7, 145.0, 136.7, 135.7, 135.4, 135.1, 133.4, 129.9, 129.6, 128.6, 128.2, 128.0, 127.8, 127.7, 127.5, 127.2, 126.4, 123.3, 120.6, 120.3, 115.2, 115.1, 113.4, 112.0, 109.2, 105.4, 105.0, 95.6, 71.0, 56.2, 55.7, 55.4, 55.2, 42.4, 28.6, 26.7, 19.8.

MS (ESI) m/z: 875 $(M+1)^+$.

Rf: 0.45 (hexane:dichloromethane:Et_2O, 5:5:2).

Compound **238**

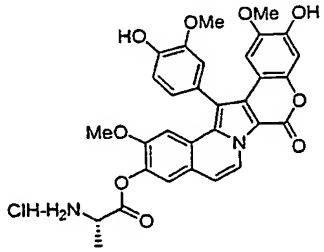


General Procedure **C** (starting from the corresponding protected lamellarin) to afford **238** as a yellow solid (5 mg, 15%).

^1H NMR (300 MHz, CD_3OD) δ 9.10 (d, J = 7.3 Hz, 1H), 7.43 (d, J = 7.3 Hz, 1H), 7.40 (d, J = 1.9 Hz, 1H), 7. 30 (dd , J = 7.3, 1.9 Hz, 1H),7.16 (s, 1H), 7.14-7.12 (m, 2H), 6.86 (s, 1H), 6.73 (d, J = 7.3 Hz, 1H), 4.61 (br s, 1H), 3.84 (s, 3H), 3.49 (s, 6H), 1.63 (d, J = 7.3 Hz, 1H).

MS (ESI) m/z: 572 $(M+1)^+$.

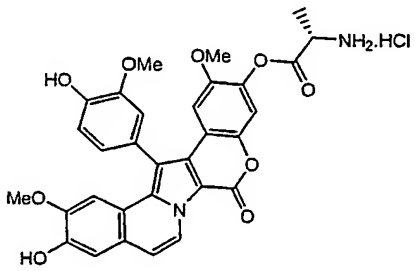
Compound **239**



To a solution of **234** (10 mg, 0.016 mmol) in anhydrous THF (1 mL) at -78°C, 0.03 mL of a 1M TBAF solution in THF and 0.7M acetic acid solution were added. The mixture was stirred for 15 min at -78°C. Sodium bicarbonate saturated solution was added (5 drops), the mixture was diluted with dichloromethane (2 mL), dried over sodium sulfate and concentrated to dryness. To the resulting residue, a cold 3.0M solution of HCl in ethyl acetate (1 mL) was added and the mixture was stirred at 0°C for 1 hour. The reaction was concentrated and the residue was washed with hexane and dichloromethane to afford **239** as a white solid (4 mg, 63% yield).

^{1}H NMR (300 MHz, CD_3OD) δ 8.99 (d, J=7.8 Hz, 1H), 7.50 (d, J=2.0 Hz, 1H), 7.48 (d, J=8.8 Hz, 1H), 7.30 (dd, J=2.0, 7.8 Hz, 1H), 7.15-7.00 (m, 3H), 6.77 (s, 1H), 6.68 (d, J=7.3 Hz, 1H), 4.52 (q, J=7.3 Hz, 1H), 3.89 (s, 3H), 3.50 (s, 3H), 3.56 (s, 3H), 3.49 (s, 3H), 1.81 (d, J=7.3 Hz, 3H).
MS (ESI) m/z: 571 $(M+1)^+$.

Compound **240**



To a solution of the corresponding protected lamellarin (47 mg, 0.047 mmol) in anhydrous THF (5 mL) at -78°C, 0.14 mL of a 1M TBAF solution in THF and 0.7M acetic acid solution were added. The mixture was stired 15 min at -78°C. Sodium bicarbonate saturated solution was added (5 drops), the mixture was diluted with

dichloromethane (2 mL), dried over sodium sulfate and concentrated to dryness. To the resulting residue, a cold 3.0M solution of HCl in ethyl acetate (1.3 mL) was added and the mixture was stirred at 0°C for 1 hour. The reaction was concentrated and the residue was washed with hexane and dichloromethane to afford **240** as a white solid (4 mg, 14 %).

^{1}H NMR (300 MHz, CD_3OD) δ 9.10 (d, J = 7.5 Hz, 1H), 7.48 (m, 2H), 7.33 (m, 1H), 7.15 (m, 3H), 6.85 (s, 1H), 6.71 (d, J = 7.5 Hz, 1H), 4.51 (m, 1H), 3.87 (s, 3H), 3.50 (s, 3H), 3.49 (s, 3H), 1.80 (d, J = 7.3 Hz, 1H). MS (ESI) m/z: 572 $(M+1)^+$.

Example 2: Bioassays for antitumoral activity

The finality of these assays is to interrupt the growth of an "*in vitro*" tumor cell culture by means a continued exhibition of the cells to the sample to be testing.

Cell Lines

NAME	N° ATCC	SPECIES	TISSUE	CHARACTERISTICS
K-562	CCL-243	human	leukemia	erythroleukemia (pleural effusion)
A-549	CCL-185	human	lung	lung carcinoma "NSCL"
SK-MEL-28	HTB-72	human	melanoma	malignant melanoma
HT-29	HTB-38	human	colon	colon adenocarcinoma
LoVo	CCL-229	human	colon	colon adenocarcinoma
LoVo-Dox		human	colon	colon adenocarcinoma (MDR)

DU-145	HTB-81	human	prostate	prostate carcinoma, not androgen receptors
LNCaP	CRL-1740	human	prostate	prostate adenocarcinoma, with androgen receptors
SK-BR-3	HTB-30	human	breast	breast adenocarcinoma, Her2/neu+, (pleural effusion)
IGROV		human	ovary	ovary adenocarcinoma
IGROV-ET		human	ovary	ovary adenocarcinoma, characterized as ET-743 resistant cells
HeLa	CCL-2	human	cervix	cervix epitheloid carcinoma
HeLa-APL	CCL-3	human	cervix	cervix epitheloid carcinoma, characterized as aplidine resistant cells
PANC-1	CRL-1469	human	pancreas	pancreatic epitheloid carcinoma

Inhibition of cell growth by colorimetric assay.

A colorimetric type of assay, using sulforhodamine B (SRB) reaction has been adapted for a quantitative measurement of cell growth and viability (following the technique described by P. A. Skehan, *et al.*, *J. Natl. Cancer Inst.* **1990**, *82*, 1107-1112).

This form of assay employs 96 well cell culture microplates of 9 mm diameter (T. Mosmann *et al.*, *J. of Immunological Methods* **1983**, *65*, 55-63; G. T. Faircloth *et al.*, *J. of Tissue and Culture Methods* **1988**, *11*, 201-205).

Most of the cell lines are obtained from American Type Culture Collection (ATCC) derived from different human cancer types.

The values for mean +/- SD of data from triplicate wells are calculated. Some parameters for cellular responses can be calculated: GI = growth inhibition, TGI = total growth inhibition (cytostatic effect) and LC = cell killing (cytotoxic effect).

Tables 1 illustrates data on the biological activity of the compounds of the present invention.

Table 1: Activity data (Molar)

		DU-145	LN-caP	SKOV-3	IGROV	IGROV-ET	SK-BR-3	MEL-28	H-MEC-1
1	GI50	8,24E-06	2,77E-07	1,37E-05	4,93E-07	4,44E-07	2,37E-06	2,24E-06	6,06E-07
	TGI	1,18E-05	1,44E-06	1,88E-05	1,76E-06	1,20E-06	1,09E-05	5,04E-06	1,38E-06
	LC50	1,70E-05	7,85E-06	1,88E-05	1,88E-05	1,88E-05	1,88E-05	1,13E-05	5,72E-06
2	GI50	6,40E-08	7,27E-08	1,40E-07	8,80E-07	1,98E-06	3,14E-07	3,02E-07	6,65E-07
	TGI	1,40E-07	3,98E-07	5,10E-06	5,17E-06	8,12E-06	2,36E-06	3,66E-06	1,89E-05
	LC50	1,89E-05	1,44E-06	1,89E-05	1,89E-05	1,89E-05	1,88E-05	1,89E-05	1,89E-05
3	GI50	1,90E-08	1,23E-07	5,37E-08	2,36E-07	2,14E-07	1,06E-07	8,81E-08	1,13E-07
	TGI	7,97E-08	3,98E-07	2,40E-07	1,06E-06	1,16E-06	7,67E-07	1,77E-06	3,14E-06
	LC50	2,00E-05	1,06E-06	1,58E-05	2,00E-05	2,00E-05	7,69E-06	1,13E-05	1,55E-05
4	GI50	2,18E-07	3,32E-07		4,02E-07	5,99E-07	3,38E-07		
	TGI	6,67E-07	7,85E-07		2,00E-06	1,64E-06	7,03E-07		
	LC50	2,14E-06	1,85E-06		1,13E-05	1,31E-05	1,47E-06		
5	GI50	3,56E-08	2,23E-07		2,47E-07	2,12E-07	2,41E-07	6,29E-08	
	TGI	1,19E-07	1,05E-06		8,55E-07	1,06E-06	5,95E-07	2,49E-07	
	LC50	5,75E-07	3,62E-06		4,54E-06	6,09E-06	3,54E-06	1,12E-06	
6	GI50	3,55E-07	5,78E-07		9,63E-07	1,39E-06	5,48E-07	3,86E-07	
	TGI	1,46E-06	7,96E-06		7,96E-06	7,96E-06	2,56E-06	1,74E-06	
	LC50	7,96E-06	7,96E-06		7,96E-06	7,96E-06	7,96E-06	7,96E-06	
7	GI50	9,93E-07	4,25E-07		1,23E-06	1,86E-06	1,14E-06	6,52E-07	
	TGI	2,31E-06	1,36E-06		2,67E-06	4,58E-06	2,61E-06	1,64E-06	
	LC50	5,41E-06	3,61E-06		5,79E-06	8,14E-06	5,98E-06	3,75E-06	
8	GI50	7,03E-07	6,54E-07		4,45E-07	3,35E-06	9,15E-07	4,07E-07	
	TGI	2,60E-06	2,47E-06		2,17E-06	1,12E-05	3,04E-06	2,20E-06	
	LC50	9,43E-06	7,21E-06		1,12E-05	1,12E-05	9,19E-06	1,12E-05	
9	GI50	5,43E-08	1,74E-07		1,82E-07	1,32E-07	1,74E-07	1,34E-07	
	TGI	1,69E-07	4,22E-07		9,09E-07	9,80E-07	3,74E-07	5,16E-07	
	LC50	6,15E-07	1,38E-06		3,00E-06	4,93E-07	8,06E-07	2,11E-06	
11	GI50	3,53E-08			2,67E-07	5,53E-06	1,87E-07	2,00E-07	
	TGI	1,51E-07			1,14E-06	1,11E-05	1,20E-06	1,18E-06	
	LC50	2,78E-06			5,88E-06	1,11E-05	6,66E-06	6,18E-06	
12	GI50	2,49E-07			1,42E-06	1,09E-05	6,98E-07	1,77E-06	
	TGI	1,43E-06			3,38E-06	1,09E-05	3,45E-06	5,98E-06	
	LC50	7,07E-06			8,01E-06	1,09E-05	1,09E-05	1,09E-05	
13	GI50	8,32E-07			1,29E-06	1,96E-06	4,54E-08	3,11E-06	
	TGI	3,64E-06			4,79E-06	7,86E-06	1,13E-07	1,09E-05	
	LC50	1,24E-05			1,24E-05	1,24E-05	1,02E-05	1,24E-05	
14	GI50	5,17E-07			4,90E-07	7,45E-07	4,24E-08	1,42E-06	
	TGI	2,19E-06			2,44E-06	4,97E-06	9,88E-08	1,40E-05	
	LC50	1,40E-05			1,40E-05	1,40E-05	1,40E-05	1,40E-05	

		A-549	K-562	PANC-1	HT-29	LOVO	LOVO-DOX	HELA	HELA-APL
1	GI50	1,88E-06	8,15E-07	2,20E-06	1,88E-05	1,18E-05	8,01E-07		
	TGI	1,88E-06	2,11E-06	7,94E-06	1,88E-05	5,76E-05	7,13E-06		
	LC50	1,88E-06	2,97E-06	1,88E-05	1,88E-05	1,88E-05	1,88E-05		
2	GI50	6,74E-07	1,17E-07	9,88E-07	8,31E-06	3,98E-07	6,04E-07		
	TGI	1,89E-05	2,25E-06	6,97E-06	1,89E-05	3,02E-06	3,83E-06		
	LC50	1,89E-05	1,89E-05	1,89E-05	1,89E-05	1,60E-05	1,89E-05		
3	GI50	2,04E-08	8,69E-08	2,48E-07	5,33E-06	3,98E-07	4,20E-07		
	TGI	1,14E-06	7,91E-07	2,20E-06	1,90E-05	9,65E-07	1,67E-06		
	LC50	1,55E-05	8,15E-06	2,00E-05	2,00E-05	2,00E-06	2,00E-05		
6	GI50	5,43E-07	3,96E-07	4,80E-07	2,50E-06	4,68E-07	2,00E-06	3,38E-07	2,38E-07
	TGI	1,21E-06	9,37E-07	1,34E-06	6,03E-06	1,08E-06	5,95E-06	6,85E-07	6,81E-07
	LC50	1,00E-05	4,44E-06	5,99E-06	1,46E-05	4,36E-06	1,78E-05	1,39E-06	1,95E-06
5	GI50	1,21E-07	7,70E-08	4,18E-07	1,70E-06	3,45E-07	4,09E-07	1,24E-07	3,10E-07
	TGI	1,02E-06	1,10E-06	1,64E-06	3,24E-06	1,06E-06	1,10E-06	1,12E-06	1,71E-06
	LC50	4,65E-06	7,40E-06	4,51E-06	6,16E-06	4,14E-06	3,40E-06	3,10E-06	5,55E-06
6	GI50	4,97E-07	4,82E-07	2,46E-06	7,96E-06	2,79E-06	3,84E-06	5,84E-07	3,41E-06
	TGI	7,96E-06	5,38E-06	7,96E-06	7,96E-06	7,96E-06	7,96E-06	7,96E-06	7,96E-06
	LC50	7,96E-06	7,96E-06	7,96E-06	7,96E-06	7,96E-06	7,96E-06	7,96E-06	7,96E-06
7	GI50	9,69E-07	5,96E-07	1,36E-06	8,71E-07	2,00E-06	3,66E-06	8,30E-07	1,85E-06
	TGI	2,96E-06	2,68E-06	3,31E-06	3,31E-06	5,05E-06	8,14E-06	1,91E-06	3,66E-06
	LC50	8,14E-06	8,14E-06	8,04E-06	8,14E-06	8,14E-06	8,14E-06	4,42E-06	7,24E-06
8	GI50	7,44E-07	2,25E-07	2,31E-07	3,77E-07	1,48E-06	8,34E-06	2,76E-07	7,30E-06
	TGI	6,34E-06	1,57E-06	8,65E-07	1,12E-05	4,68E-06	1,12E-05	1,41E-06	1,12E-05
	LC50	1,12E-05	7,49E-06	1,12E-05	1,12E-05	1,12E-05	1,12E-05	7,92E-06	1,12E-05
9	GI50	3,23E-07	4,73E-08	2,00E-07	1,61E-06	2,43E-07	3,88E-07	1,07E-07	2,82E-07
	TGI	1,15E-06	3,11E-07	1,56E-06	3,28E-06	5,84E-07	1,14E-06	4,59E-07	1,23E-06
	LC50	6,76E-06	4,18E-06	4,91E-06	6,66E-06	2,30E-06	3,63E-06	4,06E-06	3,83E-06
11	GI50	1,28E-07		2,14E-07	3,84E-08	4,24E-08	1,11E-05	2,08E-07	5,23E-06
	TGI	1,54E-06		1,76E-06	1,75E-07	1,16E-06	1,11E-05	1,35E-06	1,11E-05
	LC50	1,11E-05		1,11E-05	8,23E-06	1,04E-05	1,11E-05	1,11E-05	1,11E-05
12	GI50	1,20E-06		1,62E-06	8,11E-08	1,83E-06	1,09E-05	1,66E-06	3,66E-06
	TGI	6,64E-06		8,94E-06	8,41E-07	7,41E-06	1,09E-05	7,50E-06	1,09E-05
	LC50	1,09E-05		1,09E-05	1,09E-05	1,09E-05	1,09E-05	1,09E-05	1,09E-05
13	GI50	9,06E-07		2,43E-06	3,22E-06	7,54E-07	6,75E-07	1,83E-06	2,60E-06
	TGI	1,24E-05		1,24E-05	6,39E-06	2,35E-06	3,42E-06	9,63E-06	1,21E-05
	LC50	1,24E-05		1,24E-05	1,24E-05	9,02E-06	1,24E-05	1,24E-05	1,24E-05
14	GI50	5,55E-07		1,18E-06	2,47E-06	5,97E-07	4,97E-07	1,83E-06	2,60E-06
	TGI	1,40E-05		1,40E-05	7,26E-06	2,47E-06	1,45E-06	9,63E-06	1,21E-05

	LC50	1,40E-05		1,40E-05	1,40E-05	1,40E-05	1,40E-05	1,24E-05	1,24E-05

		DU-145	LN-caP	SKOV-3	IGROV	IGROV-ET	SK-BR-3	MEL-28	H-MEC-1
15	GI50	6,85E-08	5,60E-08		8,62E-08	6,87E-06	5,61E-08	4,82E-08	
	TGI	3,08E-06	6,09E-07		2,03E-06	1,10E-05	6,35E-07	1,64E-06	
	LC50	1,10E-05	3,93E-06		9,76E-06	1,10E-05	5,84E-06	7,24E-06	
16	GI50	5,27E-08	1,31E-07		2,26E-07	2,78E-07	2,07E-07	1,38E-07	
	TGI	2,98E-07	2,65E-07		4,78E-07	5,00E-07	4,11E-07	3,04E-07	
	LC50	2,80E-06	5,34E-07		1,59E-06	8,97E-07	8,16E-07	6,69E-07	
17	GI50	4,87E-08	1,32E-07		1,05E-07	1,62E-07	8,03E-08	5,18E-08	
	TGI	2,28E-07	2,81E-07		4,05E-07	5,44E-07	2,86E-07	1,71E-07	
	LC50	2,30E-06	5,99E-07		4,93E-06	8,78E-06	1,22E-06	7,66E-07	
18	GI50	5,05E-07	3,59E-07	1,22E-06	1,31E-06	2,00E-06	4,58E-07	5,24E-07	4,94E-07
	TGI	1,41E-06	1,27E-06	2,82E-06	3,21E-06	5,14E-06	2,14E-06	1,44E-06	8,46E-07
	LC50	7,04E-06	4,27E-06	6,51E-06	7,91E-06	1,23E-05	1,05E-05	4,43E-06	2,93E-06
19	GI50	5,32E-07	9,41E-08	7,58E-07	4,06E-07	7,61E-07	1,65E-07	2,73E-07	8,07E-07
	TGI	2,16E-06	1,41E-06	2,31E-06	2,51E-06	2,54E-06	2,28E-06	1,53E-06	2,42E-06
	LC50	6,85E-06	5,37E-06	6,57E-06	9,34E-06	1,13E-05	1,40E-05	4,99E-06	7,16E-06
20	GI50	5,00E-07			5,16E-07	5,93E-07	5,48E-08	2,24E-06	
	TGI	2,36E-06			7,46E-06	1,53E-05	2,38E-07	1,53E-05	
	LC50	1,53E-05			1,53E-05	1,53E-05	1,53E-05	1,53E-05	
21	GI50	3,53E-07	1,90E-07	8,49E-07	3,15E-07	9,01E-07	3,42E-07	2,87E-07	2,81E-07
	TGI	7,03E-07	3,83E-07	1,17E-05	6,64E-07	5,18E-06	5,99E-07	4,97E-07	5,09E-07
	LC50	1,17E-05	7,75E-07	1,17E-05	9,02E-06	1,17E-05	1,17E-05	8,60E-07	9,22E-07
22	GI50	7,43E-07	5,64E-07	2,01E-07	7,87E-07	2,89E-06	2,57E-07	3,32E-07	8,56E-07
	TGI	8,10E-06	1,82E-06	2,22E-06	8,54E-06	1,36E-05	1,81E-06	3,56E-06	2,91E-06
	LC50	1,36E-05	1,36E-05	1,36E-05	1,36E-05	1,36E-05	7,16E-06	1,36E-05	1,04E-05
23	GI50	1,76E-07	1,68E-07	1,18E-08	3,30E-07	1,86E-06	3,91E-08	6,99E-08	2,19E-07
	TGI	1,62E-06	5,34E-07	3,20E-07	1,92E-06	5,82E-06	3,03E-07	8,15E-07	6,87E-07
	LC50	5,82E-06	2,34E-06	1,97E-06	5,82E-06	5,82E-06	2,85E-06	3,09E-06	2,87E-06
24	GI50	9,13E-07	9,34E-07	1,67E-06	1,23E-06	1,31E-06	6,53E-07	1,38E-06	8,06E-07
	TGI	2,94E-06	1,91E-06	3,39E-06	4,82E-06	7,13E-06	1,93E-06	2,81E-06	2,20E-06
	LC50	7,13E-06	3,89E-06	6,90E-06	7,13E-06	7,13E-06	5,58E-06	5,74E-06	5,97E-06
26	GI50	6,11E-07	7,11E-07	8,74E-07	5,04E-07	5,74E-07	9,66E-08	2,08E-06	7,98E-07
	TGI	2,94E-06	4,30E-06	5,53E-06	2,30E-06	2,08E-06	1,09E-06	7,79E-06	1,95E-05
	LC50	1,95E-05	1,47E-05	1,95E-05	1,30E-05	1,95E-05	1,36E-05	1,95E-05	1,95E-05
27	GI50	9,76E-07			1,15E-06	1,04E-05	8,81E-07	4,47E-06	
	TGI	3,95E-06			5,06E-06	1,52E-05	3,25E-06	9,35E-06	
	LC50	1,26E-05			1,52E-05	1,52E-05	1,41E-05	1,52E-05	
28	GI50	3,15E-07			1,64E-06	1,14E-05	9,41E-07	2,24E-06	
	TGI	1,47E-06			3,97E-06	1,14E-05	4,73E-06	7,28E-06	

	LC50	7,32E-06			9,61E-06	1,14E-05	1,14E-05	1,14E-05	

		A-549	K-562	PANC-1	HT-29	LOVO	LOVO-DOX	HELA	HELA-APL
15	GI50	5,41E-08	1,60E-06	1,54E-06	4,73E-08	1,68E-06	1,10E-05	5,79E-08	2,43E-06
	TGI	1,46E-06	3,91E-06	5,26E-06	1,11E-07	4,96E-06	1,10E-05	1,41E-06	5,53E-06
	LC50	1,10E-05	9,57E-06	1,10E-05	9,17E-06	1,10E-05	1,10E-05	7,81E-06	1,10E-05
16	GI50	1,78E-07	1,83E-07	2,41E-07	4,11E-07	1,96E-07	4,20E-07	1,93E-07	2,29E-07
	TGI	5,02E-07	4,45E-07	7,56E-07	9,31E-07	3,47E-07	1,03E-06	3,68E-07	5,20E-07
	LC50	3,05E-06	2,23E-06	3,34E-06	5,00E-06	6,12E-07	4,42E-06	7,03E-07	2,38E-06
17	GI50	2,07E-07	5,36E-08	2,06E-07	3,42E-07	2,16E-07	3,84E-07	1,09E-07	1,19E-07
	TGI	6,63E-07	2,77E-07	1,52E-06	6,86E-07	4,20E-07	1,33E-06	3,59E-07	3,53E-07
	LC50	8,48E-06	2,50E-06	8,53E-06	8,78E-06	8,16E-07	5,29E-06	8,78E-07	1,85E-06
18	GI50	1,61E-06	5,58E-07	9,92E-07	8,19E-07	6,64E-07	1,08E-06		
	TGI	4,00E-06	1,51E-06	3,70E-06	4,54E-06	2,37E-06	3,67E-06		
	LC50	9,99E-06	8,64E-06	1,23E-05	1,23E-05	1,23E-05	1,21E-05		
19	GI50	6,05E-07	1,84E-06	2,45E-07	1,09E-07	7,22E-07	8,74E-07		
	TGI	2,13E-06	4,62E-06	2,42E-06	2,10E-06	2,33E-06	2,72E-06		
	LC50	6,32E-06	1,16E-05	9,50E-06	7,29E-06	6,60E-06	8,03E-06		
20	GI50	5,89E-07		1,24E-06	3,58E-06	4,36E-07	5,25E-07	1,17E-06	2,09E-06
	TGI	1,53E-05		1,53E-05	1,53E-05	5,83E-06	2,06E-06	1,53E-05	1,53E-05
	LC50	1,53E-05		1,53E-05	1,53E-05	1,53E-05	1,53E-05	1,53E-05	1,53E-05
21	GI50	1,39E-06	2,86E-07	5,14E-07	5,12E-07	1,95E-06	4,97E-06		
	TGI	4,62E-06	5,82E-07	1,81E-06	1,17E-05	4,97E-06	1,17E-05		
	LC50	1,17E-05	2,39E-06	1,17E-05	1,17E-05	1,17E-05	1,17E-05		
22	GI50	8,90E-07	6,70E-07	9,76E-07	8,79E-07	4,84E-07	6,59E-06		
	TGI	7,73E-06	4,77E-06	1,36E-05	1,36E-05	2,49E-06	1,36E-05		
	LC50	1,36E-05	1,36E-05	1,36E-05	1,36E-05	1,36E-05	1,36E-05		
23	GI50	2,43E-07	2,48E-07	4,20E-07	2,90E-07	2,02E-07	1,61E-06		
	TGI	3,24E-06	1,01E-06	3,33E-06	5,82E-06	1,40E-06	4,70E-06		
	LC50	5,82E-06	3,36E-06	5,82E-06	5,82E-06	5,82E-06	5,82E-06		
24	GI50	1,55E-06	6,80E-07	1,34E-06	7,13E-06	7,49E-07	8,91E-07		
	TGI	3,37E-06	1,91E-06	6,23E-06	7,13E-06	1,78E-06	3,66E-06		
	LC50	7,13E-06	5,30E-06	7,13E-06	7,13E-06	4,28E-06	7,13E-06		
26	GI50	1,11E-06	7,85E-07	1,07E-06	9,17E-06	1,19E-06	8,67E-07		
	TGI	8,10E-06	3,41E-06	8,80E-06	1,95E-05	1,00E-05	7,63E-06		
	LC50	1,95E-05	1,61E-05	1,95E-05	1,95E-05	1,95E-05	1,95E-05		
27	GI50	5,49E-06		4,41E-06	1,44E-07	2,70E-07	1,52E-05	4,04E-06	1,30E-05
	TGI	1,52E-05		1,30E-05	2,17E-06	2,17E-06	1,52E-05	9,47E-06	1,52E-05
	LC50	1,52E-05		1,52E-05	1,52E-05	1,52E-05	1,52E-05	1,52E-05	1,52E-05

28	GI50	1,39E-06		1,91E-06	1,11E-07	6,34E-07	1,14E-05	2,76E-06	9,53E-06
	TGI	1,14E-05		1,14E-05	1,20E-06	5,16E-06	1,14E-05	9,24E-06	1,14E-05
	LC50	1,14E-05		1,14E-05	1,14E-05	1,14E-05	1,14E-05	1,14E-05	1,14E-05

		DU-145	LN-caP	SKOV-3	IGROV	IGROV-ET	SK-BR-3	MEL-28	H-MEC-1
29	GI50	1,98E-07	7,04E-08	1,79E-06	3,67E-07	5,65E-06	2,42E-07	1,55E-06	2,42E-08
	TGI	4,40E-07	1,69E-07	3,90E-06	1,66E-06	7,35E-06	5,25E-07	3,17E-06	5,26E-08
	LC50	3,90E-06	3,96E-07	7,35E-06	7,35E-06	7,35E-06	7,03E-06	6,45E-06	2,90E-07
30	GI50	5,38E-08	2,75E-07	3,48E-07	3,50E-07	4,50E-07	4,98E-07	2,51E-07	7,05E-08
	TGI	2,65E-07	1,27E-06	1,24E-06	1,47E-06	1,83E-06	1,61E-06	1,08E-06	2,41E-07
	LC50	3,84E-06	4,90E-06	5,36E-06	6,99E-06	6,63E-06	6,39E-06	4,42E-06	8,40E-07
31	GI50	3,01E-07	5,48E-07	5,24E-07	1,26E-06	1,39E-06	1,80E-06	4,82E-07	1,19E-07
	TGI	8,61E-07	1,45E-06	4,22E-06	7,62E-06	4,00E-06	7,62E-06	7,62E-06	2,60E-07
	LC50	7,62E-06	3,43E-06	7,62E-06	7,62E-06	7,62E-06	7,62E-06	7,62E-06	5,65E-07
32	GI50	1,11E-07	4,29E-07	1,86E-06	5,61E-07	6,66E-07	1,30E-06	1,35E-06	2,76E-07
	TGI	3,09E-07	1,67E-06	3,67E-06	2,06E-06	3,01E-06	3,19E-06	2,87E-06	7,23E-07
	LC50	8,57E-07	5,08E-06	7,27E-06	6,12E-06	8,76E-06	7,82E-06	6,13E-06	5,37E-06
33	GI50	1,86E-08	3,97E-08	3,91E-08	4,96E-08	7,81E-08	3,05E-08	4,11E-08	9,80E-09
	TGI	4,60E-08	1,55E-07	2,28E-07	5,00E-07	5,89E-07	1,68E-07	1,98E-07	2,14E-08
	LC50	3,67E-07	4,23E-07	5,03E-06	4,76E-06	8,83E-06	1,44E-06	2,48E-06	4,63E-08
34	GI50	1,96E-07	4,61E-07	1,27E-06	3,07E-07	2,07E-06	1,18E-06	1,36E-06	2,44E-07
	TGI	5,88E-07	1,57E-06	2,91E-06	2,11E-06	4,63E-06	3,25E-06	2,76E-06	6,53E-07
	LC50	6,50E-06	4,11E-06	6,65E-06	8,74E-06	9,10E-06	8,95E-06	5,58E-06	3,44E-06
35	GI50	3,21E-08	8,81E-08	1,13E-07	1,52E-07	1,92E-07	2,28E-07	5,46E-08	1,97E-08
	TGI	8,81E-08	4,68E-07	9,32E-07	9,07E-07	8,55E-07	6,89E-07	9,15E-07	4,03E-08
	LC50	5,76E-07	2,22E-06	3,83E-06	4,05E-06	5,45E-06	4,03E-06	2,77E-06	8,26E-08
36	GI50	1,08E-08	4,28E-08	3,92E-08	4,69E-08	7,65E-08	3,96E-08	3,19E-08	2,65E-09
	TGI	3,83E-08	1,56E-07	2,97E-07	4,09E-07	5,40E-07	2,21E-07	1,81E-07	8,60E-09
	LC50	6,68E-07	4,24E-07	5,89E-06	7,95E-06	8,78E-06	2,94E-06	2,70E-06	1,35E-06
37	GI50	6,77E-08	5,93E-07	1,62E-06	5,77E-07	3,59E-07	5,76E-08	6,23E-07	9,74E-08
	TGI	1,55E-06	2,18E-06	3,58E-06	2,17E-06	2,11E-06	2,12E-06	2,68E-06	1,26E-06
	LC50	5,62E-06	5,05E-06	7,87E-06	5,89E-06	8,04E-06	1,06E-05	7,95E-06	4,73E-06
38	GI50	5,12E-08	1,52E-07	6,84E-07	2,44E-07	1,29E-06	4,48E-07	1,65E-07	8,09E-08
	TGI	9,11E-06	5,09E-07	7,42E-06	1,07E-06	4,51E-06	4,08E-06	5,20E-07	9,11E-07
	LC50	9,11E-06	3,90E-06	9,11E-06	9,11E-06	9,11E-06	9,11E-06	9,11E-06	9,11E-06
39	GI50	1,80E-08	2,79E-08	6,34E-08	3,41E-08	5,50E-08	5,45E-08	3,39E-08	6,98E-09
	TGI	1,42E-07	2,52E-07	8,47E-06	9,31E-07	3,69E-07	1,46E-06	2,95E-07	8,47E-06
	LC50	8,47E-06	8,47E-06	8,47E-06	8,47E-06	8,47E-06	8,47E-06	8,47E-06	8,47E-06
40	GI50	1,62E-08	1,30E-07	2,84E-08	4,49E-08	8,52E-08	8,16E-07	4,12E-08	
	TGI	9,40E-08	4,47E-07	1,07E-07	3,91E-07	5,57E-07	3,25E-06	5,95E-07	
	LC50	9,48E-06	4,38E-06	9,48E-06	5,04E-06	9,48E-06	9,48E-06	9,48E-06	
41	GI50	6,79E-07	2,10E-06	5,95E-06	9,17E-08	1,88E-07	1,62E-06	1,86E-06	
	TGI	9,87E-06	6,47E-06	9,87E-06	4,92E-07	8,52E-07	4,85E-06	4,19E-06	

	LC50	9,87E-06	9,87E-06	9,87E-06	4,70E-06	9,87E-06	9,87E-06	9,43E-06	
42	GI50	3,65E-07	3,77E-07	1,24E-06	1,85E-07	2,38E-07	2,00E-06	1,23E-06	
	TGI	2,28E-06	1,41E-06	4,44E-06	5,60E-07	6,78E-07	4,01E-06	3,32E-06	
	LC50	9,46E-06	4,91E-06	9,46E-06	2,83E-06	6,62E-06	8,04E-06	8,94E-06	

		A-549	K-562	PANC-1	HT-29	LOVO	LOVO-DOX
29	GI50	1,73E-06	4,81E-07	9,78E-07	1,84E-06	2,91E-06	7,35E-06
	TGI	3,63E-06	3,46E-06	4,23E-06	5,08E-06	7,35E-06	7,35E-06
	LC50	7,35E-06	7,35E-06	7,35E-06	7,35E-06	7,35E-06	7,35E-06
30	GI50	3,41E-07	2,04E-07	8,05E-07	2,81E-06	3,83E-07	6,83E-07
	TGI	1,27E-06	1,10E-06	2,18E-06	5,06E-06	1,06E-06	1,93E-06
	LC50	6,64E-06	8,60E-06	5,64E-06	8,60E-06	3,77E-06	5,22E-06
32	GI50	4,33E-07	4,10E-07	1,96E-06	7,62E-06	1,98E-06	1,49E-06
	TGI	1,42E-06	2,47E-06	7,62E-06	7,62E-06	5,35E-06	7,62E-06
	LC50	4,60E-06	7,62E-06	7,62E-06	7,62E-06	7,62E-06	7,62E-06
32	GI50	1,53E-06	6,73E-07	3,16E-07	2,66E-06	3,92E-07	6,71E-07
	TGI	3,34E-06	2,43E-06	1,38E-06	5,30E-06	1,65E-06	2,42E-06
	LC50	7,33E-06	8,31E-06	8,76E-06	8,76E-06	6,31E-06	8,25E-06
33	GI50	3,79E-08	5,96E-09	8,92E-08	1,34E-06	1,53E-07	1,98E-07
	TGI	1,54E-07	9,18E-07	1,06E-06	3,42E-06	3,33E-07	5,58E-07
	LC50	8,83E-07	4,03E-06	8,44E-06	8,74E-06	7,26E-07	4,33E-06
34	GI50	1,47E-06	1,04E-06	3,01E-07	1,16E-06	8,40E-07	9,10E-06
	TGI	3,71E-06	2,61E-06	9,92E-07	5,39E-06	4,02E-06	9,10E-06
	LC50	9,10E-06	6,62E-06	9,10E-06	9,10E-06	9,10E-06	9,10E-06
35	GI50	5,24E-08	8,08E-08	1,78E-07	1,18E-06	2,07E-07	2,17E-07
	TGI	2,59E-07	9,75E-07	1,21E-06	2,44E-06	7,05E-07	7,37E-07
	LC50	6,09E-06	4,82E-06	3,67E-06	5,06E-06	2,60E-06	2,80E-06
36	GI50	3,28E-08	9,48E-09	1,69E-07	1,51E-06	1,58E-07	1,45E-07
	TGI	1,54E-07	1,88E-07	1,13E-06	4,08E-06	3,21E-07	5,25E-07
	LC50	1,69E-06	5,70E-06	8,78E-06	8,78E-06	6,52E-07	8,78E-06
37	GI50	1,72E-06	1,24E-08	2,15E-06	9,12E-08	1,79E-06	2,10E-06
	TGI	3,80E-06	1,97E-06	1,10E-05	2,00E-06	4,40E-06	4,60E-06
	LC50	8,38E-06	7,53E-06	1,10E-05	1,09E-05	1,08E-05	1,01E-05
38	GI50	1,34E-06	4,13E-08	4,99E-07	3,24E-08	9,11E-06	9,11E-06
	TGI	4,78E-06	1,15E-06	9,11E-06	9,11E-08	9,11E-06	9,11E-06
	LC50	9,11E-06	9,11E-06	9,11E-06	9,11E-06	9,11E-06	9,11E-06
39	GI50	4,64E-08	3,59E-08	1,64E-07	3,04E-06	3,21E-07	3,23E-07
	TGI	8,55E-07	1,08E-06	8,47E-06	8,47E-06	2,53E-06	1,81E-06
	LC50	8,47E-06	8,47E-06	8,47E-06	8,47E-06	8,47E-06	8,47E-06
40	GI50	3,16E-08	5,82E-08	2,54E-07	3,57E-06	2,23E-07	4,70E-07
	TGI	2,70E-07	9,86E-07	3,27E-06	9,48E-06	8,84E-07	3,35E-06
	LC50	9,48E-06	4,61E-06	9,48E-06	9,48E-06	6,41E-06	9,48E-06

41	GI50	2,42E-06	1,77E-06	2,48E-06	3,24E-06	3,31E-06	4,20E-06
	TGI	8,01E-06	3,76E-06	9,87E-06	8,89E-06	9,87E-06	9,87E-06
	LC50	9,87E-06	8,02E-06	9,87E-06	9,87E-06	9,87E-06	9,87E-06
42	GI50	7,35E-07	3,13E-07	7,32E-07	3,91E-06	4,63E-07	3,95E-07
	TGI	2,99E-06	1,79E-06	4,06E-06	9,46E-06	3,63E-06	2,32E-06
	LC50	9,46E-06	5,42E-06	9,46E-06	9,46E-06	9,46E-06	9,46E-06

		DU-145	LN-caP	SKOV-3	IGROV	IGROV-ET	SK-BR-3	MEL-28	H-MEC-1
43	GI50	5,74E-08		1,46E-07	4,18E-07	9,80E-08	2,12E-07	4,98E-07	
	TGI	3,01E-07		1,14E-06	2,14E-06	3,24E-06	1,10E-06	1,21E-05	
	LC50	1,21E-05		1,21E-05	8,94E-06	1,21E-05	7,90E-06	1,21E-05	
44	GI50	4,85E-08		9,88E-08	1,06E-06	1,18E-06	1,22E-07	4,80E-07	
	TGI	2,73E-07		1,15E-06	2,32E-06	3,58E-06	8,66E-07	3,21E-06	
	LC50	7,60E-06		7,60E-06	5,06E-06	7,60E-06	7,60E-06	7,60E-06	
45	GI50	1,05E-07		1,75E-07	1,57E-06	2,58E-06	4,14E-07	8,98E-07	
	TGI	5,49E-07		2,20E-06	4,12E-06	8,07E-06	1,58E-06	1,15E-05	
	LC50	1,15E-05		1,15E-05	1,09E-05	1,15E-05	1,15E-05	1,15E-05	
46	GI50	3,80E-07	2,09E-06	3,16E-06	2,77E-07	4,99E-07	1,93E-06	1,22E-06	1,95E-07
	TGI	2,19E-06	6,58E-06	9,57E-06	2,15E-06	3,03E-06	4,67E-06	9,57E-06	9,57E-06
	LC50	8,54E-06	9,57E-06	9,57E-06	9,57E-06	9,57E-06	9,57E-06	9,57E-06	9,57E-06
46	GI50	2,76E-09	6,29E-10	3,20E-09	2,54E-09	2,87E-09	1,67E-09	2,21E-09	4,19E-10
	TGI	5,71E-09	2,48E-09	9,57E-09	5,78E-09	6,57E-09	4,64E-09	4,17E-09	8,47E-10
	LC50	9,57E-09	9,57E-09	9,57E-06	9,57E-07	9,57E-06	3,21E-08	7,87E-09	3,65E-09
47	GI50	1,08E-06	8,84E-08		7,64E-07	2,07E-06	2,29E-06	2,07E-06	
	TGI	4,61E-06	1,59E-06		1,03E-05	1,03E-05	6,01E-06	1,03E-05	
	LC50	1,03E-05	5,87E-06		1,03E-05	1,03E-05	1,03E-05	1,03E-05	
53	GI50	4,53E-06	4,01E-06		1,38E-06	2,01E-05	1,99E-06	4,03E-06	
	TGI	1,23E-05	9,75E-06		2,01E-05	2,01E-05	9,49E-06	1,55E-05	
	LC50	2,01E-05	2,01E-05		2,01E-05	2,01E-05	2,01E-05	2,01E-05	
54	GI50	2,88E-06	1,71E-06		8,84E-07	6,64E-06	1,05E-06	1,53E-06	
	TGI	7,16E-06	4,34E-06		4,02E-06	1,72E-05	4,31E-06	5,70E-06	
	LC50	1,72E-05	1,11E-05		1,33E-05	1,72E-05	1,72E-05	1,72E-05	
57	GI50	3,89E-06	2,16E-06		8,47E-07	8,90E-07	3,17E-07	1,68E-06	
	TGI	1,22E-05	5,47E-06		5,88E-06	6,43E-06	5,24E-06	1,26E-05	
	LC50	1,95E-05	1,39E-05		1,95E-05	1,95E-05	1,95E-05	1,95E-05	
59	GI50	1,39E-06	1,37E-06		8,99E-07	6,32E-07	3,72E-07	1,62E-06	
	TGI	2,60E-06	2,63E-06		2,63E-06	2,04E-06	1,15E-06	3,04E-06	
	LC50	4,86E-06	5,06E-06		7,67E-06	5,98E-06	4,11E-06	5,67E-06	
60	GI50	1,18E-06	5,50E-07		6,82E-07	2,56E-06	4,91E-07	1,17E-06	
	TGI	2,65E-06	1,79E-06		3,29E-06	6,16E-06	1,64E-06	4,14E-06	

	LC50	5,97E-06	5,25E-06		9,15E-06	9,15E-06	8,58E-06	9,15E-06	
63	GI50	2,20E-06	1,13E-06	3,06E-06	9,75E-07	6,40E-07	1,57E-06	2,34E-06	2,72E-06
	TGI	5,08E-06	3,47E-06	5,84E-06	3,86E-06	2,86E-06	4,80E-06	4,87E-06	5,25E-06
	LC50	1,17E-05	9,61E-06	1,11E-05	1,46E-05	1,52E-05	1,47E-05	1,01E-05	1,01E-05
66	GI50	1,73E-06	8,90E-07	2,85E-06	1,35E-06	1,22E-06	4,34E-07	1,42E-06	1,52E-06
	TGI	3,65E-06	1,89E-06	6,28E-06	3,02E-06	2,90E-06	1,82E-06	2,55E-06	2,73E-06
	LC50	7,12E-06	4,03E-06	7,12E-06	6,75E-06	6,87E-06	7,12E-06	4,55E-06	4,93E-06
77	GI50	8,00E-07	7,51E-06	7,52E-06	5,92E-06	2,58E-07	3,53E-06	3,29E-06	2,71E-06
	TGI	3,96E-06	1,17E-05	1,17E-05	8,84E-06	1,17E-06	1,17E-05	1,01E-05	1,17E-05
	LC50	1,17E-05	1,17E-05	1,17E-05	1,17E-05	1,17E-05	1,17E-05	1,17E-05	1,17E-05

		A-549	K-562	PANC-1	HT-29	LOVO	LOVO-DOX	HELA	HELA-APL
43	GI50	1,90E-06	1,18E-07	1,49E-06	1,21E-05	6,35E-07	9,37E-07		
	TGI	1,21E-05	5,65E-07	6,57E-06	1,21E-05	3,72E-06	3,14E-06		
	LC50	1,21E-05	1,21E-05	1,21E-05	1,21E-05	1,21E-05	9,84E-06		
44	GI50	5,44E-06	1,82E-07	1,17E-06	7,60E-06	3,74E-07	6,08E-07		
	TGI	7,60E-06	6,86E-07	4,35E-06	7,60E-06	3,18E-06	2,51E-06		
	LC50	7,60E-06	5,36E-06	7,60E-06	7,60E-06	7,60E-06	7,60E-06		
45	GI50	4,35E-06	3,15E-07	2,03E-06	1,15E-05	7,71E-07	7,78E-07		
	TGI	1,15E-05	1,73E-06	9,75E-06	1,15E-05	6,71E-06	4,51E-06		
	LC50	1,15E-05	8,79E-06	1,15E-05	1,15E-05	1,15E-05	1,15E-05		
46	GI50	1,31E-06	2,25E-06	1,34E-06	2,28E-06	4,23E-06	6,57E-06		
	TGI	9,57E-06	6,53E-06	9,57E-06	9,57E-06	9,57E-06	9,57E-06		
	LC50	9,57E-06	9,57E-06	9,57E-06	9,57E-06	9,57E-06	9,57E-06		
46	GI50	2,33E-06	5,98E-10	2,94E-09	1,03E-08	3,24E-09	1,50E-08		
	TGI	9,57E-06	1,40E-09	1,15E-08	9,57E-06	9,32E-09	9,57E-08		
	LC50	9,57E-06	2,41E-09	9,57E-06	9,57E-06	9,57E-06	9,57E-06		
47	GI50	3,26E-06	5,64E-07	3,86E-06	1,25E-06	3,97E-06	8,09E-06	5,37E-07	5,75E-06
	TGI	1,03E-05	3,74E-06	1,03E-05	1,03E-05	1,03E-05	1,03E-05	4,79E-06	1,03E-05
	LC50	1,03E-05	1,03E-05	1,03E-05	1,03E-05	1,03E-05	1,03E-05	1,03E-05	1,03E-05
53	GI50	5,66E-06	1,03E-05	1,03E-06	2,17E-06	1,11E-05	2,01E-05	5,90E-07	2,01E-05
	TGI	2,01E-05	2,01E-05	9,67E-06	2,01E-05	2,01E-05	2,01E-05	1,23E-05	2,01E-05
	LC50	2,01E-05	2,01E-05	2,01E-05	2,01E-05	2,01E-05	2,01E-05	2,01E-05	2,01E-05
54	GI50	2,85E-06	3,76E-06	7,11E-07	1,52E-06	3,40E-06	1,25E-05	6,16E-07	3,83E-06
	TGI	1,51E-05	1,42E-05	2,59E-06	1,72E-05	8,94E-06	1,72E-05	2,71E-06	1,72E-05
	LC50	1,72E-05	1,72E-05	1,72E-05	1,72E-05	1,72E-05	1,72E-05	1,72E-05	1,72E-05
57	GI50	1,29E-06	2,69E-06	6,11E-07	3,49E-06	7,17E-07	8,28E-07	6,85E-07	3,68E-06
	TGI	1,95E-05	1,95E-05	9,70E-06	1,95E-05	5,30E-06	6,91E-06	5,67E-06	1,10E-05
	LC50	1,95E-05	1,95E-05	1,95E-05	1,95E-05	1,95E-05	1,95E-05	1,95E-05	1,95E-05
59	GI50	1,70E-06	1,64E-06	1,10E-06	1,97E-06	1,13E-06	5,28E-07	1,37E-06	1,88E-06

	TGI	3,29E-06	3,45E-06	3,48E-06	3,70E-06	2,53E-06	1,60E-06	2,98E-06	3,90E-06
	LC50	6,36E-06	7,27E-06	8,81E-06	6,98E-06	5,67E-06	4,56E-06	6,44E-06	8,12E-06
60	GI50	1,62E-06	6,97E-07	7,47E-07	2,42E-06	1,61E-06	2,82E-06	1,02E-06	3,49E-06
	TGI	4,63E-06	2,19E-06	4,40E-06	5,88E-06	3,58E-06	9,15E-06	2,51E-06	9,15E-06
	LC50	9,15E-06	6,87E-06	9,15E-06	9,15E-06	7,94E-06	9,15E-06	6,13E-06	9,15E-06
63	GI50	2,84E-06	2,90E-06	1,93E-06	2,92E-06	1,46E-06	9,09E-07		
	TGI	5,57E-06	6,75E-06	5,05E-06	5,70E-06	3,68E-06	2,95E-06		
	LC50	1,09E-05	1,52E-05	1,32E-05	1,11E-05	9,11E-06	9,85E-06		
66	GI50	1,86E-06	9,82E-07	1,95E-06	2,77E-06	2,19E-06	1,91E-06		
	TGI	3,46E-06	2,80E-06	7,12E-06	6,77E-06	7,12E-06	5,56E-06		
	LC50	6,43E-06	7,12E-06	7,12E-06	7,12E-06	7,12E-06	7,12E-06		
77	GI50	6,69E-06	2,13E-06	4,46E-06	1,17E-05	1,17E-05	1,02E-05		
	TGI	1,17E-05	6,15E-06	1,17E-05	1,17E-05	1,17E-05	1,17E-05		
	LC50	1,17E-05	1,17E-05	1,17E-05	1,17E-05	1,17E-05	1,17E-05		

		DU-145	LN-caP	SKOV-3	IGROV	IGROV-ET	SK-BR-3	MEL-28	H-MEC-1
84	GI50	3,41E-06	7,10E-07	4,58E-06	2,41E-06	4,26E-06	4,60E-07	2,07E-06	6,82E-07
	TGI	8,36E-06	2,01E-06	9,90E-06	6,28E-06	8,25E-06	9,50E-07	3,86E-06	1,86E-06
	LC50	9,90E-06	5,21E-06	9,90E-06	9,90E-06	9,90E-06	9,90E-06	7,21E-06	5,96E-06
92	GI50	1,49E-05	1,67E-07	7,61E-06	3,13E-06	6,85E-06	4,35E-06	4,75E-06	1,42E-05
	TGI	1,49E-05	7,10E-07	1,49E-05	6,64E-06	1,49E-05	1,16E-05	1,01E-05	1,49E-05
	LC50	1,49E-05	5,09E-06	1,49E-05	1,41E-05	1,49E-05	1,49E-05	1,49E-05	1,49E-05
93	GI50	1,28E-05	4,08E-07	6,26E-06	3,37E-06	1,17E-05	4,95E-06	4,57E-06	1,28E-05
	TGI	1,28E-05	1,27E-06	1,28E-05	7,08E-06	1,28E-05	1,28E-05	1,28E-05	1,28E-05
	LC50	1,28E-05	7,08E-06	1,28E-05	1,28E-05	1,28E-05	1,28E-05	1,28E-05	1,28E-05
94	GI50	1,31E-05	6,73E-07	8,48E-06	1,83E-06	1,59E-06	3,35E-06	2,45E-06	1,59E-05
	TGI	1,59E-05	2,87E-06	1,59E-05	5,90E-06	1,59E-05	1,24E-05	7,31E-06	1,59E-05
	LC50	1,59E-05	1,25E-05	1,59E-05	1,59E-05	1,59E-05	1,59E-05	1,59E-05	1,59E-05
96	GI50	4,26E-06		4,20E-06	1,20E-06	2,69E-06	4,17E-07	2,14E-06	3,81E-07
	TGI	9,20E-06		9,20E-06	3,01E-06	5,60E-06	1,86E-06	4,43E-06	9,20E-06
	LC50	9,20E-06		9,20E-06	7,54E-06	9,20E-06	5,47E-06	9,18E-06	9,20E-06
97	GI50	4,13E-06		6,01E-06	1,86E-07	6,78E-07	1,23E-06	2,62E-07	3,37E-08
	TGI	9,59E-06		9,59E-06	1,94E-06	3,33E-06	3,58E-06	4,71E-06	9,59E-08
	LC50	9,59E-06		9,59E-06	7,54E-06	9,59E-06	9,59E-06	9,59E-06	9,59E-06
99	GI50	9,44E-06	4,46E-06	9,44E-06	3,07E-06	9,44E-06	9,44E-06	9,44E-06	4,06E-06
	TGI	9,44E-06	8,19E-06	9,44E-06	9,44E-06	9,44E-06	9,44E-06	9,44E-06	5,48E-06
	LC50	9,44E-06	9,44E-06	9,44E-06	9,44E-06	9,44E-06	9,44E-06	9,44E-06	7,42E-06
101	GI50	1,31E-05	8,25E-06	7,91E-07	1,19E-05	1,31E-05	1,31E-05	1,31E-05	4,66E-06
	TGI	1,31E-05	1,31E-05	2,34E-06	1,31E-05	1,31E-05	1,31E-05	1,31E-05	6,99E-06
	LC50	1,31E-05	1,31E-05	5,71E-06	1,31E-05	1,31E-05	1,31E-05	1,31E-05	1,05E-05
109	GI50	2,99E-06	1,16E-06	2,49E-06	1,80E-06	9,67E-06	3,45E-06	8,85E-07	9,17E-07

	TGI	1,54E-05	1,99E-06	1,18E-05	6,08E-06	1,99E-05	8,10E-06	2,57E-06	1,99E-05
	LC50	1,99E-05	1,99E-05	1,99E-05	1,99E-05	1,99E-05	1,90E-05	1,08E-05	1,99E-05
115	GI50	1,63E-06	6,70E-07	1,10E-06	1,07E-06	1,70E-06	1,87E-06	1,45E-06	2,13E-07
	TGI	4,29E-06	1,67E-06	2,38E-06	2,58E-06	5,38E-06	3,75E-06	2,65E-06	4,52E-07
	LC50	7,78E-06	3,87E-06	5,13E-06	6,26E-06	7,78E-06	7,53E-06	4,83E-06	2,96E-06
118	GI50	1,60E-06	9,87E-07	2,02E-06	9,70E-07	8,76E-07	6,39E-07	1,65E-06	1,45E-06
	TGI	3,00E-06	2,16E-06	4,08E-06	2,30E-06	2,33E-06	2,04E-06	3,00E-06	3,06E-06
	LC50	5,64E-06	4,76E-06	8,22E-06	5,47E-06	6,17E-06	6,25E-06	5,49E-06	6,45E-06
126	GI50	2,53E-06	1,25E-06	3,48E-06	2,26E-06	3,88E-06	2,11E-06	2,93E-06	7,46E-07
	TGI	6,49E-06	2,76E-06	6,98E-06	5,32E-06	7,87E-06	5,36E-06	5,27E-06	2,25E-06
	LC50	1,29E-05	6,04E-06	1,29E-05	1,26E-05	1,29E-05	1,29E-06	9,48E-06	6,46E-06
128	GI50	1,33E-06	1,26E-06		6,39E-07	6,89E-07		1,57E-06	1,53E-06
	TGI	2,48E-06	2,69E-06		1,98E-06	2,26E-06		3,03E-06	3,16E-06
	LC50	4,62E-06	5,71E-06		5,70E-06	7,59E-06		5,86E-06	6,53E-06
134	GI50	2,12E-06	4,58E-07	7,39E-07	9,43E-07	4,82E-07	2,10E-06	1,73E-06	2,13E-06
	TGI	4,47E-06	1,34E-06	1,85E-06	2,48E-06	2,14E-06	4,34E-06	3,23E-06	6,51E-06
	LC50	8,81E-06	4,16E-06	4,26E-06	6,50E-06	7,58E-06	8,81E-06	6,04E-06	8,81E-06

		A-549	K-562	PANC-1	HT-29	LOVO	LOVO-DOX
84	GI50	2,66E-06	7,31E-07	5,01E-07	2,34E-06	4,48E-06	9,90E-06
	TGI	4,91E-06	3,30E-06	5,47E-06	9,90E-06	9,90E-06	9,90E-06
	LC50	9,03E-06	9,90E-06	9,90E-06	9,90E-06	9,90E-06	9,90E-06
92	GI50	1,49E-05	2,23E-06	5,42E-06	1,49E-05	7,52E-06	2,14E-06
	TGI	1,49E-05	1,38E-05	1,49E-05	1,49E-05	1,49E-05	5,96E-06
	LC50	1,49E-05	1,49E-05	1,49E-05	1,49E-05	1,49E-05	1,49E-05
93	GI50	8,64E-06	1,62E-06	1,28E-05	1,28E-05	1,28E-05	3,39E-06
	TGI	1,28E-05	2,65E-06	1,28E-05	1,28E-05	1,28E-05	1,17E-05
	LC50	1,28E-05	4,36E-06	1,28E-05	1,28E-05	1,28E-05	1,28E-05
94	GI50	7,19E-06	5,26E-07	2,12E-06	1,55E-05	5,70E-06	2,84E-06
	TGI	1,59E-05	1,82E-06	1,59E-05	1,59E-05	1,59E-05	8,25E-06
	LC50	1,59E-05	4,32E-06	1,59E-05	1,59E-05	1,59E-05	1,59E-05
96	GI50	4,97E-06	1,63E-06	1,68E-06	9,20E-06	2,28E-06	5,63E-07
	TGI	9,20E-06	4,43E-06	5,65E-06	9,20E-06	9,20E-06	2,07E-06
	LC50	9,20E-06	9,20E-06	9,20E-06	9,20E-06	9,20E-06	9,20E-06
97	GI50	9,59E-06	3,20E-06	4,47E-06	9,59E-06	5,28E-06	5,29E-06
	TGI	9,59E-06	6,86E-06	9,59E-06	9,59E-06	9,59E-06	9,59E-06
	LC50	9,59E-06	9,59E-06	9,59E-06	9,59E-06	9,59E-06	9,59E-06
99	GI50	9,44E-06	9,72E-07	9,44E-06	9,44E-06	9,44E-06	9,44E-06
	TGI	9,44E-06	1,48E-06	9,44E-06	9,44E-06	9,44E-06	9,44E-06
	LC50	9,44E-06	2,26E-06	9,44E-06	9,44E-06	9,44E-06	9,44E-06
101	GI50	1,31E-05	2,19E-06	1,31E-05	1,31E-05	1,31E-05	1,31E-05
	TGI	1,31E-05	3,53E-06	1,31E-05	1,31E-05	1,31E-05	1,31E-05
	LC50	1,31E-05	5,73E-06	1,31E-05	1,31E-05	1,31E-05	1,31E-05
109	GI50	5,94E-06	4,25E-07	5,70E-06	4,81E-06	9,17E-07	5,64E-06
	TGI	1,41E-05	1,99E-05	1,99E-05	1,99E-05	4,07E-06	1,35E-05

	LC50	1,99E-05	1,99E-05	1,99E-05	1,99E-05	1,99E-05	1,99E-05
115	GI50	1,65E-06	5,36E-07	2,47E-06	2,92E-06	7,03E-07	1,76E-06
	TGI	3,11E-06	2,47E-06	7,78E-06	6,46E-06	1,82E-06	4,78E-06
	LC50	5,87E-06	7,78E-06	7,78E-06	7,78E-06	4,41E-06	7,78E-06
118	GI50	1,80E-06	1,17E-06	1,08E-06	1,92E-06	1,35E-06	4,50E-07
	TGI	3,55E-06	2,77E-06	2,40E-06	3,56E-06	2,70E-06	1,30E-06
	LC50	6,99E-06	6,57E-06	5,35E-06	6,59E-06	5,43E-06	3,86E-06
126	GI50	2,98E-06	2,15E-06	2,19E-06	3,00E-06	2,56E-06	1,29E-05
	TGI	5,74E-06	4,32E-06	6,57E-06	9,22E-06	5,68E-06	1,29E-05
	LC50	2,25E-06	8,69E-06	1,29E-05	1,29E-05	1,26E-05	1,29E-05
128	GI50	1,61E-06	1,11E-06	8,88E-07	1,95E-06	8,54E-07	4,03E-07
	TGI	3,23E-06	2,98E-06	2,31E-06	3,54E-06	1,92E-06	1,49E-06
	LC50	6,45E-06	8,01E-06	5,99E-06	6,44E-06	4,30E-06	4,66E-06
134	GI50	2,55E-06	5,71E-07	2,17E-06	2,85E-06	2,05E-06	5,19E-07
	TGI	4,93E-06	4,93E-06	4,53E-06	8,81E-06	4,21E-06	1,99E-06
	LC50	8,81E-06	8,81E-06	8,81E-06	8,81E-06	8,67E-06	7,79E-06

		DU-145	LN-caP	IGROV	IGROV-ET	SK-BR-3	MEL-28	A-549	K-562
135	GI50	1,60E-06	7,83E-07	2,10E-06	5,86E-07	5,79E-07	1,67E-06	3,34E-06	1,07E-06
	TGI	3,78E-06	2,02E-06	4,68E-06	1,98E-06	2,61E-06	5,00E-06	8,76E-06	6,82E-06
	LC50	8,76E-06	4,91E-06	8,76E-06	6,33E-06	8,76E-06	8,76E-06	8,76E-06	8,76E-06
169	GI50	1,51E-08	3,73E-08	4,71E-08	4,18E-08	3,87E-08	4,64E-08	6,46E-08	6,80E-08
	TGI	9,01E-08	1,83E-07	1,92E-06	3,01E-07	1,32E-07	5,29E-07	1,14E-06	3,21E-06
	LC50	1,05E-05	1,24E-06	1,05E-05	1,05E-05	1,05E-05	1,05E-05	9,74E-06	1,05E-05
173	GI50	4,01E-08	8,15E-08	1,53E-07	1,45E-07		1,52E-07	2,60E-07	1,11E-07
	TGI	1,34E-07	2,68E-07	8,09E-07	4,28E-07		6,04E-06	6,04E-06	6,04E-06
	LC50	7,49E-07	2,55E-06	6,04E-06	6,04E-06		6,04E-06	6,04E-06	6,04E-06
180	GI50	3,59E-08	5,30E-08	5,30E-08	6,91E-08	1,81E-08	1,34E-08	2,01E-08	4,00E-08
	TGI	8,42E-08	2,27E-07	3,19E-07	5,31E-07	5,41E-08	1,26E-07	2,33E-07	1,53E-06
	LC50	1,11E-05	6,15E-07	1,11E-05	1,11E-05	1,19E-06	1,11E-05	7,26E-06	1,11E-05
181	GI50	2,49E-08	5,93E-08	3,80E-08	5,00E-08	2,06E-08	1,68E-08	1,98E-08	3,28E-08
	TGI	5,94E-08	2,37E-07	2,31E-07	3,41E-07	5,92E-08	9,56E-08	2,09E-07	4,44E-07
	LC50	1,05E-05	6,78E-07	3,20E-06	1,05E-05	8,62E-07	2,14E-06	8,18E-06	7,14E-06
182	GI50	1,08E-06	1,75E-06	2,86E-06	3,16E-06	3,65E-07	1,08E-06	9,58E-06	3,16E-07
	TGI	2,13E-05	2,13E-05	2,13E-05	2,13E-05	1,25E-06	2,13E-05	2,13E-05	4,85E-06
	LC50	2,13E-05	2,13E-05	2,13E-05	2,13E-05	1,20E-05	2,13E-05	2,13E-05	2,13E-05
188	GI50	3,19E-06	3,30E-06	5,37E-06	2,51E-06	3,60E-06	1,14E-06	1,08E-05	9,08E-07
	TGI	2,18E-05	2,18E-05	2,02E-05	1,34E-05	1,15E-05	2,18E-05	2,18E-05	4,02E-06
	LC50	2,18E-05	2,18E-05	2,18E-05	2,18E-05	2,18E-05	2,18E-05	2,18E-05	2,18E-05
190	GI50	5,75E-08	4,86E-08	1,34E-07	1,02E-07	9,22E-08	9,15E-06	1,67E-07	7,18E-08
	TGI	2,63E-07	2,97E-07	8,95E-07	1,20E-06	3,83E-07	1,07E-05	1,66E-06	7,12E-06
	LC50	1,07E-05	1,97E-06	8,32E-06	6,42E-06	2,63E-06	1,07E-05	1,07E-05	1,07E-05
191	GI50	6,21E-08	2,44E-07	4,58E-07	5,88E-07	5,55E-07	3,63E-07	5,73E-07	1,29E-07
	TGI	2,28E-07	1,48E-06	2,77E-06	6,96E-06	3,66E-06	1,17E-05	1,17E-05	1,69E-06

	LC50	1,17E-05	5,36E-06	1,17E-05	1,17E-05	1,17E-05	1,17E-05	1,17E-05	9,49E-06
193	GI50	3,33E-08	1,18E-07	7,41E-08	1,36E-07	2,27E-07	1,01E-07	6,07E-07	1,23E-07
	TGI	1,28E-07	4,91E-07	4,10E-07	4,32E-07	5,67E-07	4,97E-07	1,02E-05	3,99E-07
	LC50	4,38E-07	5,49E-06	3,48E-06	9,59E-06	1,02E-05	1,02E-05	1,02E-05	3,91E-06
195	GI50	1,37E-08	2,21E-08	2,50E-08	4,17E-08	4,55E-08	4,41E-08	1,13E-07	1,17E-08
	TGI	2,84E-08	8,64E-08	1,45E-07	2,15E-07	8,98E-08	1,59E-07	1,15E-06	4,09E-08
	LC50	5,85E-08	3,65E-07	8,55E-07	2,74E-06	8,40E-07	1,94E-06	1,10E-05	1,70E-07
196	GI50	4,14E-07	3,98E-07	6,91E-07	8,49E-07	6,54E-07	6,75E-07	1,68E-06	2,34E-07
	TGI	1,65E-06	1,45E-06	2,49E-06	3,85E-06	1,65E-06	8,99E-06	2,64E-05	6,14E-07
	LC50	1,12E-05	9,78E-06	1,65E-05	2,64E-05	2,64E-05	2,64E-05	2,64E-05	1,50E-06
199	GI50	3,73E-09	1,58E-08	1,89E-08	3,13E-08	4,66E-08	3,26E-08	6,06E-08	1,12E-08
	TGI	9,93E-09	8,92E-08	9,62E-08	1,59E-07	9,74E-08	1,51E-07	1,33E-06	5,55E-08
	LC50	3,72E-08	3,92E-07	8,73E-07	1,22E-05	8,28E-06	7,04E-06	1,22E-05	2,81E-07
204	GI50	5,63E-09	7,90E-08	2,38E-08	1,80E-08	1,51E-07	2,68E-08	3,11E-08	7,48E-09
	TGI	1,74E-08	2,29E-07	1,13E-07	1,09E-07	3,90E-07	2,43E-07	1,00E-06	2,03E-07
	LC50	4,47E-08	5,97E-07	5,26E-07	9,52E-06	1,09E-06	7,14E-06	9,52E-06	5,96E-07

		PANC-1	HT-29	LOVO	LOVO-DOX	HELA	HELA-APL
135	GI50	2,11E-06	1,15E-06	2,69E-06	3,80E-06		
	TGI	5,53E-06	4,82E-06	8,76E-06	8,76E-06		
	LC50	8,76E-06	8,76E-06	8,76E-06	8,76E-06		
169	GI50	1,52E-07	2,97E-06	1,59E-07	2,58E-07	5,57E-08	7,05E-08
	TGI	1,05E-05	1,05E-05	4,18E-07	9,22E-07	1,39E-06	5,30E-07
	LC50	1,05E-05	1,05E-05	1,42E-06	1,05E-05	4,42E-06	2,97E-06
173	GI50	4,61E-07	6,04E-06	1,15E-06	5,02E-07	1,21E-07	4,44E-07
	TGI	6,04E-06	6,04E-06	2,57E-06	6,04E-06	6,04E-06	6,04E-06
	LC50	6,04E-06	6,04E-06	5,72E-06	6,04E-06	6,04E-06	6,04E-06
180	GI50	1,30E-07	1,11E-05	5,35E-07	1,04E-07	8,06E-08	1,30E-07
	TGI	1,11E-05	1,11E-05	2,01E-06	4,98E-07	1,99E-06	1,21E-06
	LC50	1,11E-05	1,11E-05	8,51E-06	1,11E-05	1,11E-05	1,11E-05
181	GI50	8,64E-08	3,06E-06	3,31E-07	9,45E-08	4,78E-08	6,67E-08
	TGI	2,09E-06	1,05E-05	1,10E-06	4,70E-07	6,32E-07	4,77E-07
	LC50	1,05E-05	1,05E-05	1,05E-05	1,05E-05	1,05E-05	8,14E-06
182	GI50	4,85E-06	2,13E-05	2,13E-05	1,21E-06	8,52E-06	4,46E-06
	TGI	2,13E-05	2,13E-05	2,13E-05	2,13E-05	2,13E-05	2,13E-05
	LC50	2,13E-05	2,13E-05	2,13E-05	2,13E-05	2,13E-05	2,13E-05
188	GI50	5,56E-06	2,18E-05	4,50E-06	1,30E-06	1,05E-06	9,84E-07
	TGI	2,18E-05	2,18E-05	2,18E-05	2,18E-05	3,69E-06	3,16E-05
	LC50	2,18E-05	2,18E-05	2,18E-05	2,18E-05	2,18E-05	1,58E-05
190	GI50	3,76E-07	2,99E-06	2,85E-07	3,10E-07	8,33E-08	8,99E-08
	TGI	3,50E-06	1,07E-05	1,20E-06	1,37E-06	1,31E-06	1,72E-06
	LC50	1,07E-05	1,07E-05	5,46E-06	7,68E-06	3,93E-06	5,20E-06

191	GI50	1,27E-06	6,18E-06	5,13E-07	7,85E-07	9,48E-07	9,40E-07
	TGI	9,66E-06	1,17E-05	1,70E-06	1,17E-05	2,96E-06	2,52E-06
	LC50	1,17E-05	1,17E-05	7,90E-06	1,17E-05	8,63E-06	5,96E-06
193	GI50	2,78E-07	1,02E-05	3,50E-07	3,13E-07	3,50E-07	7,97E-07
	TGI	3,60E-06	1,02E-05	8,47E-07	1,02E-05	1,02E-05	1,02E-05
	LC50	1,02E-05	1,02E-05	1,02E-05	1,02E-05	1,02E-05	1,02E-05
195	GI50	5,69E-08	2,15E-06	1,50E-07	1,06E-07	5,13E-08	8,76E-08
	TGI	3,63E-07	4,31E-06	3,42E-07	5,00E-07	2,04E-07	2,34E-07
	LC50	3,11E-06	8,62E-06	7,83E-07	2,50E-06	6,33E-07	5,36E-07
196	GI50	9,57E-07	8,46E-06	7,99E-07	5,17E-07	3,51E-07	1,17E-07
	TGI	7,25E-06	2,64E-05	3,53E-06	2,64E-05	1,93E-06	5,11E-07
	LC50	2,64E-05	2,64E-05	2,64E-05	2,64E-05	2,64E-05	1,92E-06
199	GI50	3,69E-08	2,14E-06	1,28E-07	7,37E-08	2,99E-08	7,18E-08
	TGI	2,76E-07	6,71E-06	3,35E-07	4,99E-07	1,99E-07	2,42E-07
	LC50	8,08E-06	1,22E-05	8,79E-07	1,22E-05	6,51E-07	5,74E-07
204	GI50	4,47E-08	1,40E-06	1,13E-07	1,60E-07	3,69E-08	8,88E-08
	TGI	1,71E-07	3,80E-06	2,28E-07	6,34E-06	1,72E-07	2,35E-07
	LC50	3,92E-07	9,52E-06	4,63E-07	9,52E-06	4,52E-07	5,94E-07

		DU-145	LN-caP	IGROV	IGROV-ET	SK-BR-3	MEL-28	A-549	K-562
206	GI50	2,18E-08	7,52E-08	5,27E-08	2,97E-08	7,01E-08	4,40E-08	5,58E-08	3,11E-08
	TGI	3,99E-08	4,75E-07	1,94E-07	1,90E-07	4,51E-07	1,69E-07	4,10E-07	1,11E-06
	LC50	7,25E-08	3,33E-06	5,89E-07	5,89E-07	2,89E-06	1,04E-06	2,77E-06	4,23E-06
207	GI50	2,30E-08	1,27E-07	7,63E-08	4,36E-08	2,02E-07	4,44E-08	9,14E-08	9,20E-08
	TGI	4,16E-08	9,44E-07	3,18E-07	2,86E-07	1,07E-06	2,45E-07	1,02E-06	3,06E-06
	LC50	7,48E-08	4,10E-06	1,55E-06	2,38E-06	4,21E-06	4,60E-06	3,55E-06	9,26E-06
208	GI50	8,78E-06	1,46E-06	8,78E-06	8,78E-06	5,01E-06	8,78E-06	8,78E-06	
	TGI	8,78E-06	2,91E-06	8,78E-06	8,78E-06	7,97E-06	8,78E-06	8,78E-06	
	LC50	8,78E-06	5,83E-06	8,78E-06	8,78E-06	8,78E-06	8,78E-06	8,78E-06	
209	GI50	4,29E-09	1,58E-08	3,37E-08	3,17E-08	4,78E-08	3,28E-08	4,28E-08	
	TGI	1,19E-08	5,60E-08	1,24E-07	7,01E-08	6,95E-08	8,39E-08	1,95E-07	
	LC50	4,04E-08	2,33E-07	4,77E-07	3,45E-07	1,01E-07	4,80E-07	7,13E-07	
210	GI50	1,81E-07		3,17E-07	1,45E-07	3,97E-07		4,77E-07	6,12E-07
	TGI	3,39E-07		1,06E-06	3,66E-07	1,36E-06		3,94E-06	2,13E-06
	LC50	6,31E-07		3,65E-06	9,20E-07	4,59E-06		1,04E-05	6,17E-06
221	GI50	4,31E-08	7,22E-08	8,19E-08	6,48E-08	1,53E-06	1,06E-07	8,02E-08	8,83E-08
	TGI	2,57E-07	5,02E-06	2,01E-05	2,01E-05	1,29E-05	2,01E-05	2,01E-05	2,01E-05
	LC50	2,01E-05	2,01E-05	2,01E-05	2,01E-05	2,01E-05	2,01E-05	2,01E-05	2,01E-05
233	GI50	7,83E-08	1,26E-07	4,99E-08	1,07E-07		1,69E-07	3,12E-07	9,58E-08
	TGI	1,80E-07	5,57E-07	1,42E-07	7,21E-07		4,75E-06	2,06E-06	1,09E-06
	LC50	1,95E-05	3,72E-06	1,95E-05	1,95E-05		1,95E-05	1,95E-05	8,61E-06
238	GI50	4,58E-08	2,13E-06	7,99E-08	4,13E-08	1,53E-07	5,26E-08	4,58E-08	4,33E-08

	TGI	9,65E-08	1,65E-05	2,82E-07	1,44E-07	1,61E-06	3,51E-07	4,38E-07	2,47E-07
	LC50	1,65E-05	1,65E-05	1,26E-06	1,65E-05	1,65E-05	1,25E-05	1,65E-05	1,20E-06
239	GI50	5,83E-08		2,42E-07	1,61E-07	2,06E-07	2,03E-07	1,64E-07	7,86E-08
	TGI	1,31E-07		3,38E-06	4,05E-06	1,99E-06	2,60E-06	1,55E-05	2,16E-07
	LC50	1,32E-06		1,65E-05	1,65E-05	1,65E-05	1,65E-05	1,65E-05	5,29E-07
240	GI50	6,06E-08	4,09E-06	1,36E-07	8,24E-08	5,93E-08	9,97E-08	1,26E-07	1,24E-07
	TGI	1,34E-07	1,65E-05	5,22E-07	3,66E-07	3,43E-07	3,81E-07	4,70E-07	4,50E-07
	LC50	1,65E-05	1,65E-05	3,64E-06	1,29E-05	1,65E-05	1,44E-06	1,51E-06	2,09E-06

		PANC-1	HT-29	LOVO	LOVO-DOX	HELA	HELA-APL
206	GI50	1,37E-07	1,32E-06	1,67E-07	2,94E-07	5,05E-08	8,34E-08
	TGI	1,27E-06	1,05E-05	3,31E-07	1,01E-06	3,30E-07	5,23E-07
	LC50	6,25E-06	1,05E-05	6,60E-07	6,37E-06	1,93E-06	2,82E-06
207	GI50	1,27E-07	3,77E-06	1,89E-07	3,16E-07	4,22E-08	7,79E-08
	TGI	2,37E-06	9,26E-06	4,05E-07	2,85E-06	1,23E-06	1,50E-06
	LC50	9,26E-06	9,26E-06	8,68E-07	9,26E-06	3,34E-06	3,71E-06
208	GI50	5,92E-06	8,78E-06	8,78E-06	8,78E-06	2,08E-07	1,54E-07
	TGI	8,78E-06	8,78E-06	8,78E-06	8,78E-06	6,18E-07	3,85E-07
	LC50	8,78E-06	8,78E-06	8,78E-06	8,78E-06	2,31E-06	1,14E-06
209	GI50	6,74E-08	3,38E-06	1,19E-07	1,37E-07	6,62E-08	8,27E-08
	TGI	2,82E-07	9,99E-06	2,51E-07	4,88E-07	2,69E-07	2,21E-07
	LC50	1,03E-06	1,05E-05	5,27E-07	2,60E-06	1,01E-06	5,17E-07
210	GI50	3,98E-07	7,09E-06	2,05E-06	2,43E-06	6,11E-07	5,16E-07
	TGI	1,51E-06	1,04E-05	3,99E-06	6,04E-06	5,54E-06	3,08E-06
	LC50	4,87E-06	1,04E-05	7,76E-06	1,04E-05	1,04E-05	1,04E-05
221	GI50	7,86E-08	2,01E-05	2,41E-06	2,83E-06	5,64E-08	7,96E-08
	TGI	2,01E-05	2,01E-05	6,20E-06	1,42E-05	2,01E-05	2,01E-05
	LC50	2,01E-05	2,01E-05	1,59E-05	2,01E-05	2,01E-05	2,01E-05
233	GI50	3,41E-07	1,95E-05	5,45E-07	1,05E-06	1,91E-07	4,17E-07
	TGI	1,95E-05	1,95E-05	1,31E-06	1,54E-05	3,82E-06	3,15E-06
	LC50	1,95E-05	1,95E-05	1,95E-05	1,95E-05	1,60E-05	1,43E-05
238	GI50	2,54E-08	2,65E-06	5,70E-08	2,26E-06	5,22E-08	1,57E-07
	TGI	2,50E-07	1,06E-05	2,26E-07	8,98E-07	1,31E-07	5,16E-07
	LC50	1,61E-06	1,65E-05	1,29E-06	1,65E-05	1,24E-06	1,76E-06
239	GI50	2,32E-07	1,08E-05	6,92E-07	8,71E-07	2,34E-07	6,56E-07
	TGI	1,10E-05	1,65E-05	2,87E-06	1,65E-05	3,61E-06	4,18E-06
	LC50	1,65E-05	1,65E-05	1,65E-05	1,65E-05	1,65E-05	1,65E-05
240	GI50	7,05E-08	1,64E-06	1,70E-07	4,61E-07	5,75E-08	3,41E-07
	TGI	6,82E-07	1,59E-05	5,09E-07	1,15E-06	1,49E-07	1,40E-06
	LC50	8,86E-06	1,65E-05	1,52E-06	1,65E-05	1,40E-06	7,61E-06

Example 3: Topoisomerase I inhibition

The marine alkaloid lamellarin D (LAM-D, **3**) has been recently characterized as a potent poison of human topoisomerase I endowed with remarkable cytotoxic activities against tumor cells. We report here the structure-activity relationship study in the LAM-D series.

Two groups of triester compounds incorporating various substituents on the three phenolic OH at positions 8, 14 and 20 of 6*H*-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-*a*]isoquinolin-6-one pentacyclic planar chromophore typical of the parent alkaloid were tested as topoisomerase I inhibitors.

Compounds incorporating amino acid residues strongly promoted DNA cleavage by human topoisomerase I. LAM-D derivatives tri-substituted with leucine, valine, proline, phenylalanine or alanine residues, or a related amino side chain, stabilize topoisomerase I-DNA complexes. The DNA cleavage sites detected a T↓G or C↓G dinucleotides with these molecules were identical to that of LAM-D (**3**) but slightly different from those seen with camptothecin which stimulates topoisomerase I-mediated cleavage at T↓G only.

With prostate (DU-145 and LN-CaP), ovarian (IGROV and IGROV-ET resistant to ecteinascidin-743) and colon (LoVo and LoVo-Dox cells resistant to doxorubicin) cancer cells (but not with HT29 colon carcinoma cells), the most cytotoxic compounds correspond to the most potent topoisomerase I poisons. The observed correlation between cytotoxicity and topoisomerase I inhibition strongly suggests that

topoisomerase I-mediated DNA cleavage assays can be used as a guide to the development of superior analogs in this series.

Two assays, based on DNA relaxation and DNA cleavage (Bailly, C. DNA relaxation and cleavage assays to study topoisomerase I inhibitors. *Methods Enzymol.* **2001**, *340*, 610-623) were used evaluate the effects of the lamellarin analogs on the catalytic activity of human topoisomerase I.

In the first assay, a supercoiled plasmid DNA was relaxed with topoisomerase I in the absence or presence of the test compounds, each tested at 1 μM. DNA relaxation products were then resolved by gel electrophoresis on agarose gels containing ethidium bromide to stain the DNA. The alkaloid camptothecin, used as a positive control, strongly promotes DNA cleavage by topoisomerase I. Similarly, the intensity of the band corresponding to nicked DNA is significantly amplified in the presence of LAM-D (**3**) indicating that this natural product also stabilizes DNA-topoisomerase I covalent complexes. This functional assay is useful to identify the topoisomerase I poisons among the various analogs synthesized. The analogous compounds with a 5-6 saturated bond (**11**, **22**, **108**, **109**, **139**) were inactive in this assay.

Different cationic groups, mostly amino acid residues, were incorporated at the three phenoxy positions of LAM-D. A marked inhibition of topoisomerase I was observed with the positively charged molecules **40** (Ala), **39** (Leu), **36** (Val), **33** (Pro) and **25** (Phe) but not with the corresponding NH-Boc derivatives or the non-planar C5-C6 analogues. The Phe derivative is significantly less potent than the other amino acid derivatives which are all more or less equally effective at inhibiting topoisomerase I. The stereospecificity was investigated with the Val derivatives for which we compared the activity of the (*L*)

(**36**, **38**, **135**, **144**) and (*D*) (**17**, **32**, **34**, **122**) isomers but there was no difference between the two series. Compound **17** and **36** both stimulated DNA cleavage by the enzyme. No effect was observed with the Boc-protected analogs in the C5-C6 double stranded (**38**, **122**) or C5-C6 single-stranded (**32**, **34**, **135**, **144**) series. The amino compounds **24** and **169** were also found to inhibit topoisomerase I.

Concentration-dependent measurements were performed with each of the positive compounds identified and a few representative gels comparing the anti-topoisomerase I activity of LAM-D (**3**) with the three analogues Val(*D*) (**17**), Pro (**33**) and the amino compound **169** were done. This later compound is equally efficient to (**3**) in terms of stimulation of DNA cleavage by topoisomerase I. In all cases, the dose-response analysis confirmed that the cationic LAM-D analogues potently inhibit the enzyme.

It is clear that the introduction of an amino acid functionality on the phenolic OH groups at positions 8, 14 and 20 of LAM-D (**3**) is not detrimental to topoisomerase I inhibition. The extent of topoisomerase I-mediated DNA cleavage is fully maintained when a Leu, Val, Ala or Pro residue is incorporated on the LAM-D skeleton whereas a non charged group abolishes the anti-topoisomerase I activity. A phenylalanine residue is much less favorable than a proline or an alanine residue for example. The observations that the incorporation of a cationic group promoted topoisomerase I inhibition suggested that the enhanced capacity of the drugs to bind to DNA could be responsible for a better enzyme inhibition.

A second assay, based on the cleavage of a radiolabeled DNA substrate by topoisomerase I, was used to confirm that the cationic lamellarin derivatives do effectively function as topoisomerase I poisons. A 117-bp

DNA restriction fragment uniquely end-labeled at the 3' end was subjected to cleavage by topoisomerase I in the presence of the different compounds and the resulting DNA cleavage products were resolved on sequencing-type polyacrylamide gels. The advantage of this assay is to detect the cleavage sites and to locate their positions with nucleotide resolution, providing thus information on the site selectivity of cleavage.

The reference drug CPT products three sites at nucleotide positions 26, 48 and 81 which all three correspond to T$^{\downarrow}$G sites. Cleavage at TG sites in the presence of CPT is believed to result from the interaction of topoisomerase I with the T residue combined with the stacking of the CPT molecule with the adjacent G residue. A fourth weak site can be detected at the top of the gels (T$^{\downarrow}$G107).

The sequence selectivity profiles are slightly different with the lamellarin analogs. LAM-D is less efficient than CPT for topoisomerase I-mediated DNA cleavage at sites T$^{\downarrow}$G48 and T$^{\downarrow}$G81 but it induces an additional cleavage site at C$^{\downarrow}$G73. This likely reflects a different mode of interaction with the topoisomerase I-DNA covalent complexes.

Cleavage profiles identical to that of **3** were obtained with the cationic derivatives such as **39** (Leu), **36** (Val), **33** (Pro) and **25** (Phe) but not with the corresponding NH-Boc derivatives or the non-planar C5-C6 analogue. The amino compounds **169** and **7** were also found to stimulate DNA cleavage by the enzyme and here also we found no difference between the (*L*) (**36**) and (*D*) (**17**) Val isomers. The results are thus entirely consistent with those obtained by the relaxation assay and therefore validate the conclusion that the cationic lamellarin derivatives potently inhibit topoisomerase I.